original contributions

Survey of US Medical Oncologists' Practices and Beliefs Regarding *DPYD* Testing Before Fluoropyrimidine Chemotherapy

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QUESTION ASKED: What are the major factors deterring medical oncologists in the United States from ordering *DPYD* testing before fluoropyrimidine (FP) treatment?

SUMMARY ANSWER: Most medical oncologists in the United States do not order pretreatment *DPYD* testing because dihydropyrimidine dehydrogenase (DPD) deficiency is relatively rare and because clinical practice guidelines have not recommended pretreatment testing.

WHAT WE DID: We conducted a survey of medical oncologists in the United States who are members of relevant SWOG committees regarding their practices and beliefs around pretreatment *DPYD* testing.

WHAT WE FOUND: Of the 59 US medical oncologists who completed the survey, only 32% strongly or somewhat agree that pretreatment *DPYD* testing is useful to inform FP treatment, 20% have ever ordered pretreatment testing, and 3% order testing for at least 10% of their FP-treated patients. The most important factors that deter oncologists from ordering testing were low prevalence of DPD deficiency (54%) and lack of clinical practice guideline recommendations (48%).

BIAS, CONFOUNDING FACTOR(S), REAL-LIFE IMPLICATIONS: The reader should keep in mind that this survey represents the views of a relatively small number of medical oncologists who participate in SWOG, and may not reflect the views of the medical oncology community in the United States. Additionally, this short survey did not differentiate between *DPYD* genotype testing and DPD phenotype testing or between complete and partial DPD deficiency, which may complicate interpretation of some questions. Nevertheless, these results confirm that pretreatment *DPYD* testing is rare in the United States and that testing recommendations from clinical guidelines would dramatically increase clinical adoption, as has been seen throughout Europe.

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ASSOCIATED CONTENT

Appendix

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

Accepted on February 7, 2022 and published at ascopubs.org/journal/op on March 3, 2022: Full-length article available online at DOI https://doi.org/10.1200/OP.21.00874

CARE DELIVERY

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abstract

PURPOSE Patients who carry reduced-activity *DPYD* polymorphisms have increased fluoropyrimidine (FP) toxicity risk. Although pretreatment *DPYD* testing is recommended throughout most of Europe, it is not recommended in the United States, and adoption has been limited. The objective of this survey was to describe the current practice in the United States regarding pretreatment *DPYD* testing and understand the factors deterring oncologists from ordering testing.

METHODS Survey invitations were e-mailed to 325 medical oncologists practicing in the United States who are members of the SWOG Cancer Research Network Gastrointestinal Cancer, Breast Cancer, or Early Therapeutics Committees. Descriptive statistics were used to evaluate survey responses.

RESULTS Responses were collected from 59 (18.2%) US medical oncologists, of whom 98% strongly or somewhat agree that patients with dihydropyrimidine dehydrogenase (DPD) deficiency have increased toxicity risk and 96% would modify FP dosing for a patient with known DPD deficiency. However, only 32% strongly or somewhat agree that pretreatment *DPYD* testing is useful to inform FP treatment, 20% have ever ordered pretreatment testing, and 3% order testing for at least 10% of their FP-treated patients. The most important factors that deter oncologists from ordering testing were low prevalence of DPD deficiency (54%) and lack of clinical practice guideline recommendations (48%).

CONCLUSION Clinical adoption of pretreatment *DPYD* testing is extremely limited in the United States. Utilization may be substantially increased by inclusion in the oncology clinical practice guideline recommendations, coverage through health insurance, and potentially education of medical oncologists regarding available treatment modification guidelines.

JCO Oncol Pract 18:e958-e965. © 2022 by American Society of Clinical Oncology

INTRODUCTION

The fluoropyrimidines (FP), fluorouracil and its oral analog capecitabine, are antimetabolite chemotherapy agents widely used for the treatment of various solid tumors and have served as a backbone of chemotherapy regimens for more than 60 years.[1] These agents are recommended within National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for the management of colon, rectal, pancreatic, biliary tract, gastric, head and neck, ovarian, and breast cancers.[2-8] Although generally well tolerated, up to 30% of patients treated with FP experience severe toxicity such as diarrhea, nausea, mucositis, myelosuppression, neurotoxicity, and hand-foot syndrome, which can lead to treatment-related death in up to 1% of patients.[9]

Dihydropyrimidine dehydrogenase (DPD) is the primary enzyme responsible for metabolic elimination of the FP.[1] Polymorphisms in *DPYD*, the gene encoding DPD, reduce DPD activity. Patients who carry pathogenic *DPYD* variants have partial or complete loss of DPD activity and are at increased risk of severe FP toxicity. In Caucasians, approximately 6% of patients inherit at least one nonfunctional or reduced-function allele, leading to partial DPD deficiency and approximately 0.2% inherit two nonfunctional alleles leading to complete DPD deficiency, whereas about approximately 8% of African Americans have partial or complete DPD deficiency.[10,11]

More than 300 *DPYD* variants have been identified[12] and at least four variants (*DPYD*2A [c.1905+1G>A]*, *DPYD*13 [c1679T>G]*, *p.D949V [c.2846A>T]*, and *HapB3 [c.1129-5923C>G, c.1236G>A]*) have been

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 7, 2022 and published at ascopubs.org/journal/op on March 3, 2022: DOI https://doi.org/10.1200/OP.21.00874

confirmed to increase risk of severe FP toxicity.[13,14] The increased risk of FP toxicity is acknowledged in the US Food and Drug Administration (FDA) labeling of these drugs[15,16] and in the NCCN guidelines for colon cancer treatment.[2] FP dose reduction in carriers of *DPYD* variants has been prospectively demonstrated to reduce severe toxicity and health care costs.[17-19] The Clinical Pharmacogenetics Implementation Consortium (CPIC), an interdisciplinary group that develops evidence-based clinical practice guidelines for pharmacogenetic-guided medication therapy, recommends 50% dose reduction in *DPYD* intermediate metabolizers and recommends > 90% reduction or avoiding FP therapy in poor metabolizers.[20]

On the basis of the strong evidence of clinical benefit, pretreatment *DPYD* testing is recommended by European Society of Medical Oncology (ESMO) guidelines[21] and is recommended or required throughout most of Europe.[22-24] However, pretreatment *DPYD* testing is not recommended by the FDA[15,16] or any national oncology practice guidelines in the United States such as NCCN and ASCO,[2,22] and thus, test adoption is believed to be limited.[25] The objective of this survey was to identify US medical oncologists' current practices and beliefs regarding pretreatment *DPYD* testing and understand the factors deterring medical oncologists from ordering the test.

METHODS

Survey Development

The initial draft survey to collect information about *DPYD* testing practices and beliefs was created in Qualtrics (Provo, UT) by the study team. Questions and response choices were reviewed by medical oncologists within the University of Michigan Rogel Cancer Center and revised on the basis of feedback. The revised survey was submitted to the SWOG Survey Committee for further review and revision before final approval.

Sample Selection and Survey Distribution

The SWOG Cancer Research Network is composed of more than 12,000 members of diverse oncology professions practicing in a variety of oncology practice settings. On April 5, 2021, the SWOG Operations Office sent e-mail survey invitations to 325 US-based medical oncologists who are members of the Gastrointestinal Cancer, Breast Cancer, or Early Therapeutics Committees. Two e-mail reminders were sent approximately 3 weeks apart, before closing the survey on May 28, 2021. This study was exempt from human subject research by the University of Michigan Institutional Review Board (IRBMED). All participants agreed to participate by completing the survey. No compensation was offered for survey completion.

Survey Analysis

Descriptive statistics were calculated to evaluate survey responses. The results are reported as n (%) or median (interquartile range [IQR], range). Exploratory subgroup analysis was conducted to compare the difference in responses to selected questions between academic and nonacademic practices using the chi-square test using GraphPad Prism (San Diego, CA).

RESULTS

Survey Respondents

A total of 59 survey responses were initiated and partially completed and 54 completed surveys were collected, with an overall response rate of 18.2%. The primary practice settings of the responding oncologists were academic teaching institution/hospital (83%) or community hospital cancer center or specialty outpatient cancer care site (13%; Appendix Table A1, online only). The most common primary field of practice was gastrointestinal oncology (60%) followed by breast oncology (34%). The median number of years in practice was 13.5 years (IQR: 14 years, range: 2-39 years). The median number of patients the medical oncologist started on a new chemotherapy regimen containing either 5-FU or capecitabine in the past 6 months was 20 (IQR: 37, range: 0-100).

DPYD Testing Before or After Starting Fluoropyrimidine-Based Chemotherapy

Twenty percent of oncologists (n = 12) indicated they had ever ordered *DPYD* testing before starting FP chemotherapy, including 17% (n = 10) who rarely order pretreatment testing (< 10% of patients) and 3% (n = 2) who order testing for 10%-49% of patients. Alternatively, 78% of oncologists have ordered testing after starting FP treatment.

Perspective on DPD Deficiency

There was general agreement among the oncologists that patients with DPD deficiency are at increased risk of toxicity from FP chemotherapy. The majority of oncologists strongly agree (72%) with the statement, and no oncologists selected somewhat disagree or strongly disagree (Fig 1A). There was also general agreement that DPD deficiency is actionable information. For a patient starting FP chemotherapy who was known to be DPD-deficient, 65% of medical oncologists would decrease dosing, whereas only 4% would continue with treatment without any modification (Table 1).

Beliefs About Pretreatment *DPYD* Testing

There was less agreement among oncologists regarding the usefulness of pretreatment *DPYD* testing, with only 32% strongly or somewhat agreeing (Fig 1B). The two most important factors that deter oncologists from ordering pretreatment *DPYD* testing were low prevalence of DPD deficiency (54% indicated this factor was extremely or very important) and lack of clinical practice guidelines that recommend testing (48%; Fig 2). Exploratory subgroup analysis did not find any differences in these reasons

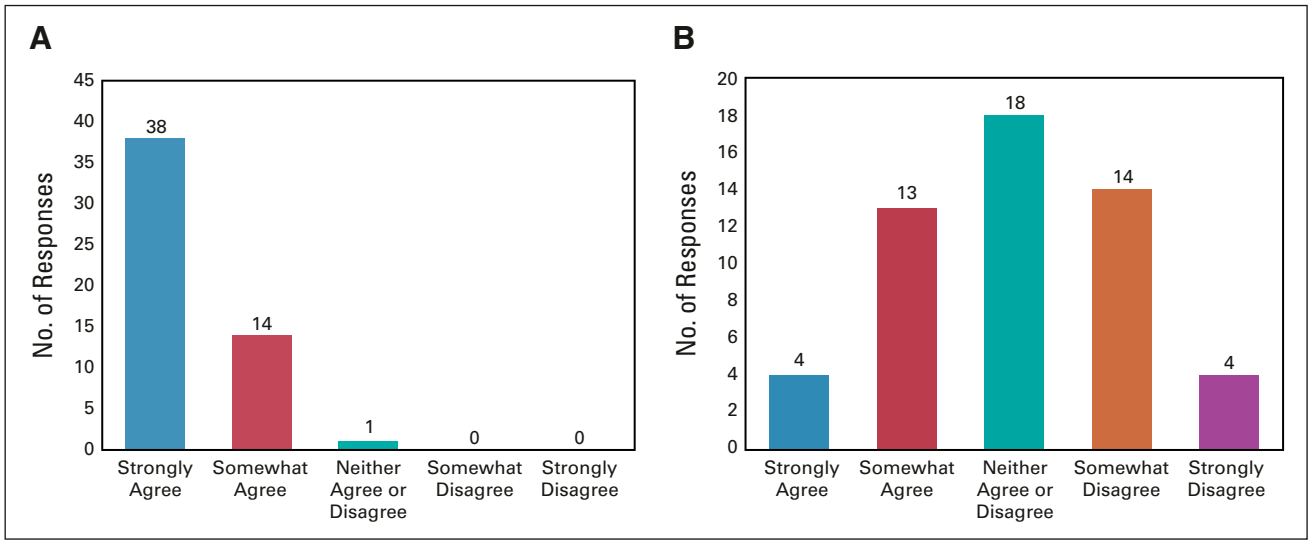

FIG 1. Perspective of oncologists on DPD deficiency and pretreatment *DPYD* testing. Histogram of agreement to the prompts: (A) patients with DPD deficiency are at increased risk of toxicity from fluoropyrimidine chemotherapy and (B) pretreatment DPD testing is useful. DPD, dihydropyrimidine dehydrogenase.

between medical oncologists who worked in academic versus nonacademic settings (all $P > .05$, data not shown).

DISCUSSION

Patients who carry reduced-activity *DPYD* polymorphisms have a higher risk of severe toxicity from FP chemotherapy.[13,14,17] Despite the known clinical benefits of pretreatment *DPYD* testing in reducing severe FP toxicity and decrease in overall health care costs,[18,19] testing has not been recommended in the United States. The objective of this survey was to describe the current practice of US-based medical oncologists regarding pretreatment *DPYD* testing and understand the factors preventing oncologists from ordering testing. As expected, adoption of pretreatment *DPYD* testing is limited; only 20% of oncologists have ever ordered testing before FP treatment and only 3% routinely do so in their practices. Although there was near-uniform agreement that *DPYD* genotype information is actionable, pretreatment testing is not believed to be useful because of the low prevalence of DPD deficiency and lack of clinical practice guidelines that recommend testing. Although complete DPD deficiency is rare (approximately 0.2%), partial DPD deficiency is common (approximately 6%) and is also associated with unacceptable rates of severe (> 50%) and fatal (2%-4%) toxicity.[10,26]

In this survey, lack of clinical practice guidelines that recommend testing was the second most important factor preventing pretreatment *DPYD* testing. The significance of this factor has been found in surveys conducted in other countries. In a survey conducted in France before a national requirement for pretreatment testing, lack of recommendations from medical societies/health authorities was one of the main arguments for limited *DPYD* screening, along with delays in obtaining results and lack of adequate reimbursement by the health insurance system.[27] In the Netherlands, national guidelines for colon cancer were updated in 2017 to recommend pretreatment *DPYD* genotyping. This update to treatment guidelines increased the percentage of patients who received pretreatment *DPYD* testing from 1% to 87%.[28] Clinical adoption of pretreatment *DPYD* testing in the United States would be expected to substantially increase if national oncology practice guidelines such as NCCN and ASCO recommended testing.

The NCCN colon cancer guidelines panel does not support universal pretreatment *DPYD* genotyping because of a concern that FP dose reduction in *DPYD* carriers may reduce treatment efficacy.[29,30] Our survey found that concern of decreasing efficacy is not a major concern of

TABLE 1. Starting FP-Based Chemotherapy in DPD-Deficient Patient

Response Selected	No. (%)
Decrease FP dosing	35 (65)
Switch to non-FP treatment	7 (13)
I do not know and would likely consult a colleague or guideline for appropriate treatment	7 (13)
Increase toxicity monitoring without changing dosing	3 (6)
I would not change their treatment on the basis of DPD status	2 (4)

Abbreviations: DPD, dihydropyrimidine dehydrogenase; FP, fluoropyrimidine.

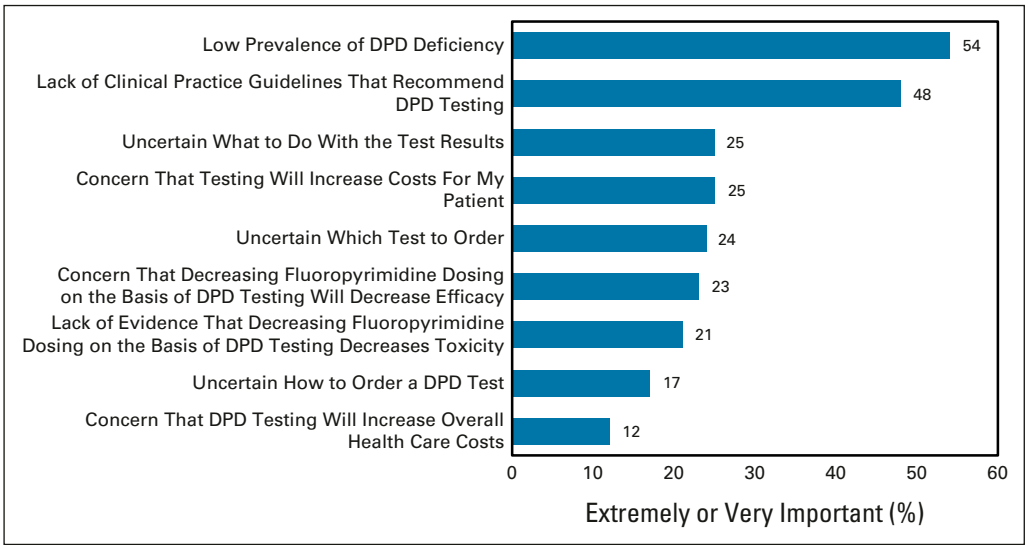

FIG 2. Factors deterring oncologists from ordering *DPYD* testing. Factors that deter oncologists from ordering *DPYD* testing before starting fluoropyrimidine chemotherapy in descending order of importance (combined percentage of extremely or very important). Multiple options could be selected. DPD, dihydropyrimidine dehydrogenase.

medical oncologists regarding pretreatment *DPYD* testing (23% extremely/very important). This may be due to evidence that FP dose reduction in patients with DPD deficiency results in comparable exposure to wild-type patients receiving standard FP doses,[18,19] and no evidence of efficacy reduction has been detected.[31,32] Nevertheless, further validation of the clinical utility of pretreatment *DPYD* testing, specifically the noninferiority of efficacy, within prospective randomized-controlled trials may be necessary for national oncology practice guidelines to support pretreatment testing.

The third most important factor preventing pretreatment testing was the lack of understanding of what to do with the test results (25% extremely/very important). CPIC publishes expert consensus treatment guidelines for dosing FP in patients with known *DPYD* genotype. Most medical oncologists indicated they would decrease dosing (65%) or switch to a non-FP (13%) in a DPD-deficient patient, consistent with the guideline recommendations. However, it is unclear whether medical oncologists are aware of CPIC guidelines, as prior studies have found low levels of awareness of CPIC guidelines across medical specialities.[33-35] The other two education-related factors, including which test to order (24%) and how to order the test (17%), were somewhat lower in the rankings of importance, potentially because of medical oncologists' familiarity and prior experience with ordering *DPYD* testing after treatment started (78%). The National Center for Biotechnology Information Genetic Testing Registry is a searchable resource to find companies offering Clinical Laboratory Improvement Amendments–approved *DPYD* testing options.

Increasing costs for patients was the fourth most important factor (25%), whereas increasing overall health care costs was the least important factor. Pretreatment *DPYD* testing is slightly cost-saving (~$50-60 US dollars/patient),[18,19] primarily because of the prevention of severe toxicity that can require costly hospital admissions.[36] Pretreatment testing is covered by Medicare across most of the United States and by some, but not all, private insurance providers.[37] Increasing insurance coverage of *DPYD* testing could further increase clinician acceptance of pretreatment testing.

This was the first survey, to our knowledge, to describe the current practice and perspectives of US medical oncologists regarding *DPYD* testing. Distribution via SWOG enabled broad inclusion of oncologists from across the United States in various practice settings and specialties in which FP treatments are indicated. However, the results of this survey are limited by the number of respondents (n = 54) and the low overall response rate (18.2%), which may overrepresent medical oncologists who have strong beliefs about or understanding of ordering *DPYD* testing. The survey also represents views of oncologists who are SWOG members, who may be more familiar with clinical practice guidelines or in some other way different from the general population of medical oncologists in the United States. Additionally, these results may not be representative of all oncology specialties or practice settings, as 83% of respondents practiced in academic teaching hospitals. Finally, to minimize survey burden, the survey questions did not differentiate between *DPYD* genotype testing and DPD phenotype testing or between complete and partial DPD deficiency, which may have affected some responses and complicated interpretation of some questions.

In conclusion, *DPYD* testing before FP treatment in the United States is limited, despite evidence of clinical benefit, reduction in overall health care costs, and acceptance by

international clinical guidelines. Adoption in the United States would likely be substantially increased by inclusion of pretreatment *DPYD* testing within the oncology clinical practice guidelines. However, this may require further validation of clinical utility and possibly confirmation of noninferiority in *DPYD* variant carriers who receive reduced FP dose within prospective randomized clinical trials. Uniformity in insurance coverage and clinical education regarding *DPYD* testing options and interpretation would also enhance adoption of pretreatment testing in the United States to ensure safe and effective FP treatment in patients with cancer.

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DISCLAIMER

The funding bodies played no role in the design of the study, analysis, and interpretation of data and in writing the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or SWOG.

PRIOR PRESENTATION

Presented in preliminary form at Pharmacogenomics Global Research Network-American Society of Human Genetics (PGRN-ASHG) Symposium (virtual), October 8, 2021; American Society of Health-System Pharmacists (ASHP) Midyear Conference (virtual), December 8, 2021.

SUPPORT

This survey was developed in collaboration with the SWOG Symptom Control and Quality of Life and Digital Engagement Committees and SWOG Survey Subcommittee, which are supported in part by NIH/NCI grants CA180888 and CA180819.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.21.00874.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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ACKNOWLEDGMENT

The authors would like to thank the members of the SWOG Gastrointestinal Cancer, Breast Cancer, and Early Therapeutics Committees who completed our survey.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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N. Lynn Henry
Research Funding: Blue Note Therapeutics (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov/physician/27894/summary

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Consulting or Advisory Role: Celgene, Halozyme, Newlink Genetics, Ipsen, Incyte, QED Therapeutics, Klus Pharma, AstraZeneca, GlaxoSmithKline, Rafael Pharmaceuticals, Histosonics
Research Funding: Celgene (Inst), Celgene (Inst), Bristol Myers Squibb (Inst), Agios (Inst), Incyte (Inst), Clovis Oncology (Inst), Debiopharm Group (Inst), FibroGen (Inst), Halozyme (Inst), MedImmune (Inst), Rafael Pharmaceuticals (Inst), Ipsen (Inst), Exelixis (Inst), Syros Pharmaceuticals (Inst), Relay Therapeutics (Inst), Pancreatic Cancer Action Network (Inst), Actuate Therapeutics (Inst)
Travel, Accommodations, Expenses: ASCO, FibroGen, FibroGen

Daniel L. Hertz
Research Funding: Disarm Therapeutics
Uncompensated Relationships: PEPID, Saladax Biomedical

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Primary Practice Setting and Primary Field of Respondents

Category	Selection	No. (%)
Primary practice setting (n = 53)	Academic teaching institution/hospital	44 (83)
	Community hospital cancer center or specialty outpatient cancer care site	7 (13)
	Outpatient oncology office	1 (2)
	Health maintenance organization (HMO)	1 (2)
Primary field (n = 53)	Gastrointestinal oncology	32 (60)
	Breast oncology	18 (34)
	General oncology	2 (4)
	Head and neck oncology	1 (2)