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Global Investigation of Clinical Implementation Strategies for *DPYD* Testing to Guide Fluoropyrimidine Therapy

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ABSTRACT

Fluoropyrimidines are a vital component of chemotherapy regimens. Deleterious *DPYD* variants reduce activity of dihydropyrimidine dehydrogenase, the rate-limiting enzyme of fluoropyrimidine catabolism, resulting in reduced fluoropyrimidine clearance and elevated risk of life-threatening toxicities. *DPYD* genotype-guided fluoropyrimidine therapy can mitigate the risk of severe life-threatening toxicities, but adoption of testing globally has been limited. We developed a 91-item survey investigating global *DPYD* implementation strategies to gain insight into common practices and successful strategies. The survey was disseminated to Pharmacogenomics Global Research Network Implementation Working Group members consisting of 54 health care sites across 15 countries. Survey responses were received from 28 sites (52%) across 9 countries. Over 80% of sites implemented, or planned to implement, a preemptive testing strategy (i.e., before a fluoropyrimidine is administered) leveraging the electronic health record (EHR) to disseminate *DPYD* results to providers. All sites created infrastructure to support *DPYD* testing (e.g., order sets, EHR decision support), but 70% of sites indicated reliance on clinicians to remember test ordering. Only 2 sites reported high *DPYD* testing rates (> 75%) among patients planned to receive a fluoropyrimidine. Most sites (57%) used in-house

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clinical laboratories that tested for the majority of *DPYD* Tier 1 variants. Among sites that had implemented *DPYD* testing, the median turnaround time was 10 days. Few sites indicated that a high percentage (>75%) of *DPYD* results were returned before fluoropyrimidine administration. Our results suggest that additional implementation strategies are needed, addressing barriers and facilitators of *DPYD* testing.

Study Highlights

- What is the current knowledge on the topic?
 - An estimated 2 million patients worldwide receive a fluoropyrimidine yearly. Studies have shown that 60%–80% of patients who carry a deleterious *DPYD* variant and receive standard fluoropyrimidine dosing experience severe, life-threatening toxicities. *DPYD* genotype-guided fluoropyrimidine therapy can mitigate the risk of life-threatening toxicities, but adoption of testing globally has been limited.
- What question did this study address?
 - We developed a global survey investigating *DPYD* implementation strategies to gain insight into the landscape of *DPYD* testing and identify common practices and implementation strategies that may be applicable worldwide.
- What does this study add to our knowledge?
 - Similar to prior studies, we found that numerous strategies were used to promote *DPYD* testing. Despite these efforts, testing penetrance was low (<25%) at most sites. Even when *DPYD* testing was performed, a minority of sites indicated that a high percentage (>75%) of *DPYD* results were returned before a fluoropyrimidine was administered. Only 14% of sites reported having a titration protocol as part of *DPYD* implementation strategies. These novel findings were consistent across international sites. Of interest, there were global differences in dosing recommendations for a *DPYD* AS of 1.5, whereby sites reported no dose reduction, dose reduction of 50%, 25%, or a range of 25%–50%. Our results show that efficient workflows are needed to increase testing penetrance, ensure timely return of results, and integrate titration protocols into clinical practice. Additionally, further research is needed to refine dosing recommendations for select *DPYD* variants.
- How might this change clinical pharmacology or translational science?
 - Successful *DPYD* implementation strategies can help promote the adoption of testing for the safe and effective use of fluoropyrimidines.

types, with an estimated 2 million patients worldwide receiving a fluoropyrimidine each year [1, 2]. Fluoropyrimidines are highly effective anti-cancer drugs; however, their use is associated with serious, potentially life-threatening toxicities including diarrhea, stomatitis, hand-foot syndrome, and neutropenia [3–5]. The occurrence of severe toxicities can be as high as 30% among a general population of patients receiving a systemic fluoropyrimidine, dependent on dosage and method of administration (e.g., bolus versus continuous infusion) [4, 6].

DPYD encodes for dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme responsible for approximately 80% of fluoropyrimidine catabolism [7, 8]. Deleterious *DPYD* variants reduce DPD enzymatic activity, resulting in reduced fluoropyrimidine clearance and elevated risk of life-threatening toxicities [9–12]. Studies have estimated that the occurrence of severe toxicities is between 60% and 80% for those harboring a deleterious *DPYD* variant and receiving a standard fluoropyrimidine dose [10, 13–16]. Furthermore, mortality risk can be up to 25 times greater among *DPYD* variant carriers [17, 18].

Clinical guidelines are available that provide recommendations for initial fluoropyrimidine dose reductions based on *DPYD* results [9, 14, 19]. In particular, results are translated to an activity score (AS) that ranges from 2 (normal DPD activity) to 0 (little to no DPD activity), with each score linked to a specific therapeutic recommendation [9]. Guidelines also highlight the importance of titration to a higher fluoropyrimidine dose if the initial *DPYD*-guided dose reduction is tolerated to help prevent under exposure [9, 14]. Numerous studies have demonstrated that *DPYD*-guided fluoropyrimidine therapy can mitigate the risk of severe toxicities and treatment-related death [20–23]. There is also emerging evidence showing *DPYD*-guided therapy does not negatively impact anti-cancer efficacy, though for certain *DPYD* variants (e.g., HapB3 haplotype) additional research is needed to optimize initial dose reductions and subsequent titration [24, 25]. Despite strong evidence supporting *DPYD*-guided fluoropyrimidine therapy, adoption of testing has been slow globally and varies by region and country. *DPYD* testing is standard of care among many European countries, supported by the European Medicine Agency (EMA) recommending pre-treatment DPD testing [26]. Outside of Europe, *DPYD* testing has been limited in part due to lack of clinical or regulatory guidelines that recommend or require pre-treatment testing [13, 14, 27, 28]. Nevertheless, there have been early adopters of *DPYD* testing across the globe [29].

Previous surveys have explored implementation strategies for adopters of *DPYD* testing, but those efforts either focused on specific regions of the world, specific use case scenarios (e.g., pre-treatment testing only), or did not fully assess multiple domains of implementation [26, 30]. Herein, we developed a

1 | Introduction

Fluoropyrimidines, which include intravenous 5-fluorouracil (5-FU) and its oral prodrugs capecitabine and tegafur, are a vital component of chemotherapy regimens to treat various cancer

comprehensive, global survey investigating *DPYD* implementation strategies inclusive of patient populations undergoing testing, penetrance of testing (i.e., extent to which *DPYD* genotyping was performed), workflow considerations, clinical integration, and educational approaches. This survey aimed to gain insight into the international landscape of *DPYD* testing and identify common practices and successful implementation strategies that may be applicable worldwide.

2 | Methods

A 91-item survey was developed by the Pharmacogenomics Global Research Network (PGRN) Implementation Working Group [29]. The survey was modeled after previously published data collection tools and adapted to capture *DPYD* implementation strategies globally [30–32]. Given that irinotecan is frequently prescribed with fluoropyrimidines, the survey also assessed *UGT1A1* implementation strategies, which will be reported in a future manuscript [33]. The survey was approved as non-human subject research by the University of Florida, Moffitt Cancer Center, and University of Cincinnati Institutional Review Boards.

Survey data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted at the University of Florida [34]. The survey tool was pilot-tested by international PGRN Implementation Working Group members for clarity and feasibility prior to dissemination. The survey was disseminated to PGRN Implementation Working Group members, consisting of 54 unique health care sites across 15 countries, on May 17, 2024, and closed to responses on September 30, 2024. Sites that had implemented or planned to implement *DPYD* were eligible to complete the survey. Implementation was defined as *DPYD* testing for clinical use and having infrastructure in place to support test ordering and application to patient care (Data S2). Survey responses were curated to ensure only one response was provided from each site. If contradictory or missing information was identified, survey respondents were contacted for clarification. Descriptive statistics were used to analyze responses.

3 | Results

3.1 | Site Characteristics

Survey responses were received from 28 of 54 sites (52% response rate) across 9 countries. Twenty sites were in the US with one site each from the remaining 8 countries (Figure S1). Site characteristics are summarized in Table 1 and Table S1. Seventy-nine percent of sites were academic institutions. Nineteen sites (68%) had implemented, and another nine (32%) had developed infrastructure to implement but had not started *DPYD* genotyping (i.e., planning stage). All sites reported using *DPYD* results to guide 5-FU and capecitabine therapy, while three sites also used results to guide tegafur dosing. Almost half of respondents (46%) indicated that *DPYD* testing was performed for patients diagnosed with any cancer type anticipated to receive a fluoropyrimidine. The rest indicated that testing was performed only for select cancer types with colorectal being the most selected

TABLE 1 | Summary of site characteristics ($n=28$).

Location, n (%)	
US	20 (71)
Non-US	8 (29)
Type of institution, n (%)	
Academic	22 (79)
Community health center	2 (7)
Academic-community hybrid	2 (7)
Other (e.g., governmental institution non-governmental organization)	2 (7)
Stage of implementation, n (%)	
Implemented	19 (68)
Planning	9 (32)
Indication of testing–cancer diagnosis, n (%) ^a	
Any cancer diagnosis planned to start fluoropyrimidine	13 (46)
Colorectal	13 (46)
Pancreatic	8 (29)
Breast	8 (29)
Gastric	8 (29)
Hepatobiliary	6 (21)
Esophageal	5 (18)
Other or unknown	4 (14)
Indication of testing–type of fluoropyrimidine, n (%) ^a	
5-FU	28 (100)
Capecitabine	28 (100)
Tegafur	3 (11)
Flucytosine	1 (4)

^aSurvey question allowed for selection of multiple answers.

indication. The majority of US sites (65%), but none of the non-US sites, indicated that a precision medicine or pharmacogenetics program led implementation efforts. Pharmacy (18%), medical oncology (14%), and molecular pathology (7%) were also reported as leading *DPYD* implementation across sites.

3.2 | *DPYD* Pre-Test Workflows

Most sites (82%) reported that a preemptive *DPYD* testing approach (or planned approach) best described their implementation strategy, with preemptive defined in the survey as testing performed before the start of fluoropyrimidine therapy (Table 2). Two sites indicated that reactive testing, defined in the survey as testing after starting a fluoropyrimidine (e.g., in response to reported toxicity) best described their *DPYD* testing approach, while three sites reported using both testing strategies. Among sites performing preemptive testing ($n=23$), 30%

TABLE 2 | *DPYD* pre-test workflows or anticipated workflows.

<i>DPYD</i> test ordering, n (%)	All (n = 28)	US (n = 20)	Non-US (n = 8)
Preemptive	23 (82)	17 (85)	6 (75)
Both preemptive and reactive ^a	3 (11)	2 (10)	1 (13)
Reactive	2 (7)	1 (5)	1 (13)
Timing of <i>DPYD</i> ordering if preemptive, n (%)	All (n = 23)	US (n = 17)	Non-US (n = 6)
Variable depending on the clinician/clinic/patient	8 (35)	6 (35)	2 (33)
Initial visit for a cancer diagnosis	7 (30)	6 (35)	1 (17)
At time of fluoropyrimidine prescribing	6 (26)	4 (24)	2 (33)
Unknown/missing	2 (9)	1 (6)	1 (17)
Test ordering workflow if preemptive, n (%) ^b	All (n = 23)	US (n = 17)	Non-US (n = 6)
Clinician (e.g., physician, nurse, pharmacist) responsible for remembering to order	16 (70)	12 (71)	4 (67)
Integrated into clinical workflows (e.g., paper or EHR order set)	12 (52)	8 (47)	4 (67)
Interruptive (i.e., pop-up) alert in the EHR	6 (26)	5 (29)	1 (17)
Other ^c	1 (4)	1 (6)	0 (0)

^aThree sites selected 'other' approach described as both preemptive and reactive.

^bSurvey question allowed for selection of multiple answers.

^cOne site indicated *DPYD* testing is part of a preemptive pharmacogene panel performed at diagnosis of any disease.

indicated *DPYD* testing was ordered (or planned to be ordered) at the initial visit for cancer diagnosis, and 26% reported test ordering at the time of fluoropyrimidine prescribing. Thirty-five percent (8 of 23 sites) reported that timing of preemptive test ordering was variable, dependent on the clinician and/or patient. Timing of *DPYD* test ordering did not vary greatly between US and non-US sites.

Respondents indicated that numerous strategies were utilized for *DPYD* test ordering (Table 2). For sites with a preemptive testing strategy, 70% indicated that workflows depended on clinicians remembering to order testing. Fifty-two percent of sites integrated *DPYD* test order into paper and/or electronic health record (EHR) order sets, and 26% reported using interruptive EHR clinical decision support (CDS) to prompt testing. A slightly higher percentage of US sites utilized interruptive EHR CDS, whereas a higher percentage of non-US sites integrated *DPYD* testing into clinical workflows. Sites in the planning stage created workflows that depended less on clinicians remembering to order *DPYD* testing (Table S2). Almost half of sites (44%) planning to implement indicated workflows will include interruptive CDS to prompt *DPYD* testing compared to 16% of sites that had already implemented using interruptive CDS.

3.3 | *DPYD* Testing

A similar number of sites used (or planned to use) a multi-gene pharmacogenetics panel, *DPYD* single gene test, or both as part of the implementation strategy (Table 3; Table S2). In-house testing was performed or planned by 57% of sites, followed by use of commercial laboratories (29%). Commercial laboratories were

less commonly used for testing among non-US sites. Insurance billing was the primary source of support for *DPYD* testing, with 71% of sites billing (or planning to bill) for reimbursement (Table S3). Insurance billing was enriched for US sites (90%) compared to non-US sites (25%). Other support or planned support included patient out-of-pocket payment (32%), research funding (29%), and institutional support using non-research funds (18%). Non-US sites were enriched for using research funding and institutional resources to support *DYPD* testing (Table S3).

Most sites genotyped, or planned to genotype, for the majority of *DPYD* Tier 1 variants as defined by the Association for Molecular Pathology (AMP) [12]. Specifically, *DPYD* *2A, *13, and c.2846A>T were tested, or planned to be tested, by 100%, 93%, and 89% of sites, respectively (Table 3; Table S2). Additionally, the variant common in persons of African ancestry (p.Y186C, rs115232898) was tested, or planned to be tested, by 75% of sites. Sites in the planning stage selected genotyping platforms that test for a greater number of Tier 1 variants (Table S2). Less than 30% of sites tested, or planned to test, for Tier 2 variants. Over 30% of sites tested for additional variants (Table 3; Table S4). The *HapB3* causal variant (c.1129-5923C>G) and c.1236G>A tag were tested, or planned to be tested, by 75% and 57.1% of sites, respectively. Three sites, one US and two non-US, tested for the c.1236G>A tag variant only. One site indicated that *DPYD* HapB3 haplotype variant selection may be reevaluated, and another site stated a disclaimer may be added when only the c.1236G>A tag variant is tested and not the causal c.1129-5923C>G variant (Table S5).

Twenty-four sites reported *DPYD* genotyping turnaround time, including five sites in the planning stage that provided anticipated turnaround time. The median time to receive results

TABLE 3 | *DPYD* testing approach or planned testing approach.

Parameter	All (n = 28)	US (n = 20)	Non-US (n = 8)
<i>DPYD</i> test platform, n (%)			
Multi-gene	10 (36)	8 (40)	2 (25)
Both multi-gene and single-gene	10 (36)	7 (35)	3 (38)
Single-gene	8 (29)	5 (25)	3 (38)
<i>DPYD</i> assay, n (%) ^a			
In-house by a clinical laboratory	16 (57)	11 (55)	5 (63)
Commercial laboratory	8 (29)	7 (35)	1 (13)
Another healthcare institution's clinical laboratory	4 (14)	3 (15)	1 (13)
Research laboratory	2 (7)	0 (0)	2 (25)
Source of DNA for genotyping, n (%) ^a			
Blood	24 (86)	17 (85)	7 (88)
Buccal	9 (32)	7 (35)	2 (25)
Saliva	3 (11)	1 (5)	2 (25)
Tumor	0 (0)	0 (0)	0 (0)
Tier 1 variants tested, n (%) ^{b,c,d}			
*2A (c.190511G>A, rs3918290)	28 (100)	20 (100)	8 (100)
*13 (c.1679T>G, rs55886062)	26 (93)	19 (95)	7 (88)
c.2846A>T (rs67376798)	25 (89)	19 (95)	6 (75)
p.Y186C (c.557A>G, s115232898)	21 (75)	16 (80)	5 (62)
HapB3 (c.1129-5923C>G, rs75017182)	21 (75)	16 (80)	5 (62)
HapB3 (c.1236G>A, rs56038477)	16 (57)	10 (50)	6 (75)
c.2279C>T (rs112766203)	2 (7)	1 (5)	1 (13)
c.868A>G (rs146356975)	1 (4)	0 (0)	1 (13)
Tier 2 variants tested, n (%) ^{b,c,d}			
*7 (c.295_298delTCAT, rs72549309)	8 (29)	5 (25)	3 (38)
*8 (c.703C>T, rs1801266)	8 (29)	6 (30)	2 (25)
c.1774C>T (rs59086055)	2 (7)	1 (5)	1 (13)
c.1314T>G (rs186169810)	1 (4)	0 (0)	1 (13)
c.1475C>T (rs72549304)	1 (4)	0 (0)	1 (13)
c.2639G>T (rs55674432)	1 (4)	0 (0)	1 (13)
Sites that tested additional variants, n (%)			
Others	9 (32)	6 (30)	3 (38)
*10 (c.2983G>T, rs1801268)	8 (29)	6 (30)	2 (25)

^aSurvey question allowed for selection of multiple answers.

^bTier defined per Association for Molecular Pathology [12].

^cOne non-US site selected whole genome sequencing and thus would include all *DPYD* Tier 1 and Tier 2 variants.

^dOne non-US site stated *DPYD**2A and HapB3 haplotype are tested preemptively with gene sequencing performed for reactive testing. For that site only *DPYD**2A and HapB3 haplotype variants were included in this table since all patients independent of preemptive or reactive strategy would be tested for these variants.

among the sites that had implemented was 10 calendar days, with a range of 2 days to > 15 days (Table S6). Turnaround time was generally similar when *DPYD* testing was performed by a

commercial laboratory or through an in-house clinical laboratory, though in-house testing reported the quickest turnaround time of 2 days (Table S6).

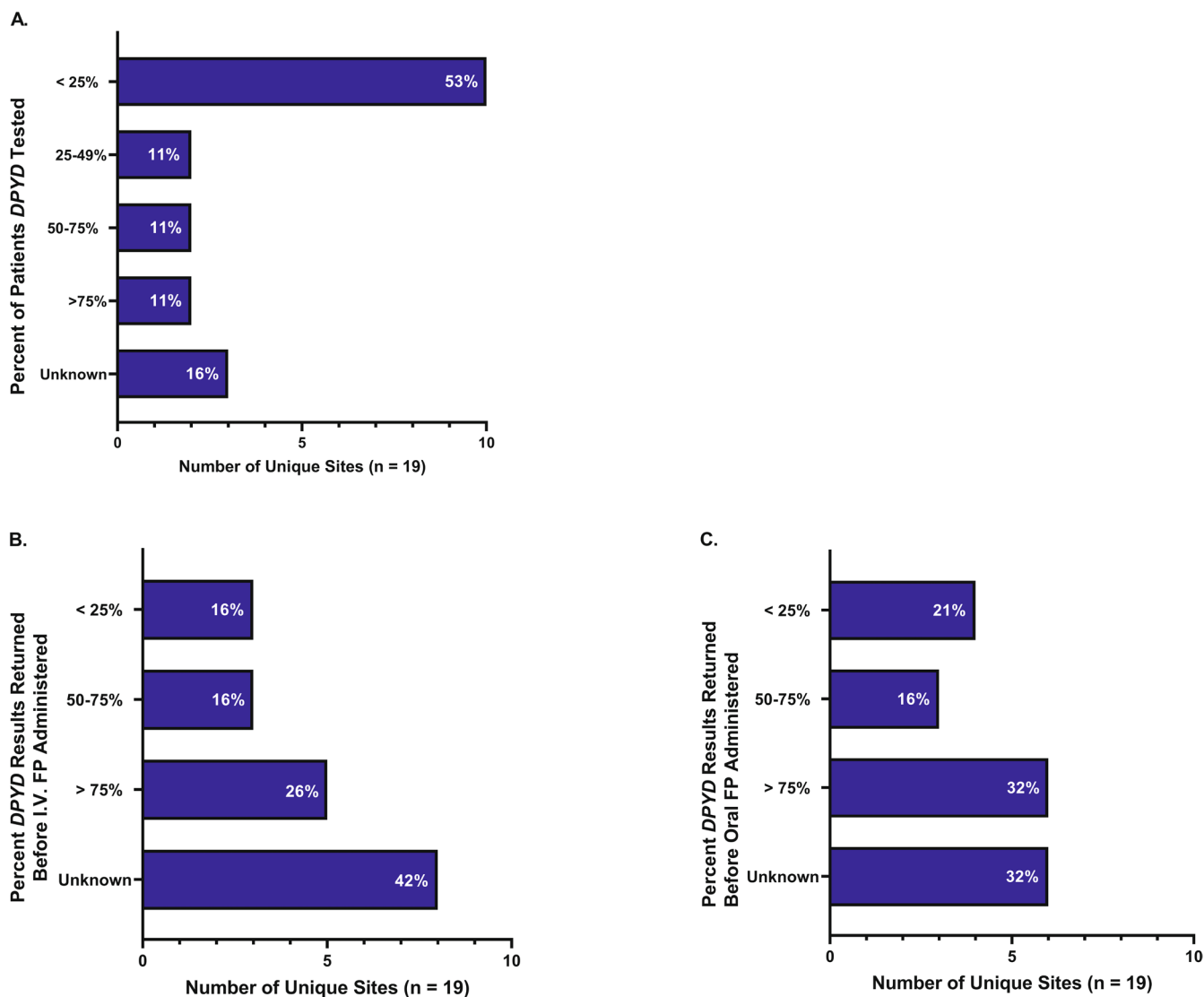


FIGURE 1 | (A) Percent of eligible patients who are DPYD genotyped; Percent of results returned before either (B) intravenous (I.V.) or (C) oral fluoropyrimidine (FP) was administered.

Among the 19 sites that had already implemented *DPYD* testing into patient care, most indicated that testing was performed on less than 25% of patients planned to receive a fluoropyrimidine, indicating low penetrance (Figure 1A; Figure S2). Only two sites indicated that greater than 75% of patients who received a fluoropyrimidine were tested. There were no strong correlations between *DPYD* pre-test strategies and the percent of patients who were genotyped; however, test ordering at the time of fluoropyrimidine prescribing potentially led to higher testing rates (Table S7). Among patients undergoing *DPYD* testing, a minority of sites indicated that a high percentage (> 75%) of *DPYD* results were returned before a fluoropyrimidine was administered (Figure 1B,C; Figure S3). There were no obvious differences between *DPYD* pre-test strategies, test turnaround time, and having a high percent of results returned before fluoropyrimidine administration (Table S8). All sites that integrated *DPYD* test ordering into clinical workflows (e.g., order sets or interruptive CDS) reported $\geq 50\%$ of results returned before fluoropyrimidine administration.

Almost half of sites (45%) that had implemented *DPYD* testing into patient care indicated that *UGT1A1* genotyping accompanied *DPYD* testing over 75% of the time (Figure S4A). A higher percentage of US sites (53%) reported *UGT1A1* genotyping accompanied *DPYD* testing over 75% of the time when compared to non-US sites (20%; Figure S4B).

3.4 | *DPYD* Post-Test Workflows

Numerous strategies were used, or planned to be used, across sites for returning results to providers (Table 4). While most sites (82%) returned, or planned to return, *DPYD* results to providers as discrete data within their EHR, other methods included laboratory documents (e.g., PDF), laboratory portals, electronic messages through the EHR or email, and pharmacogenetic consult notes. Numerous individuals were responsible, or planned to be responsible, for interpreting test results, with over 50% of sites indicating a precision medicine or pharmacogenetics program, pharmacist, and oncologist were all responsible for test interpretation

TABLE 4 | *DPYD* post-test workflows or anticipated workflows.

Parameter	All (n = 28)	US (n = 20)	Non-US (n = 8)
Results return to providers through health records, n (%) ^a			
Discrete data in EHR capable of driving CDS	23 (82)	18 (90)	5 (63)
Laboratory document (e.g., PDF) placed in paper health record or EHR	18 (65)	15 (75)	3 (38)
Consultation note placed in paper health record or EHR	11 (39)	11 (55)	0 (0)
EHR-based inbox messaging	9 (32)	9 (45)	0 (0)
Other ^c	2 (7)	2 (10)	0 (0)
Results return to providers through other tools, n (%) ^a			
Lab portal accessible by the provider	4 (14)	1 (5)	3 (38)
Email or fax	2 (7)	1 (5)	1 (13)
Other ^d	2 (7)	0 (0)	2 (25)
Guideline/source used for <i>DPYD</i> -guided therapeutic recommendations, n (%)			
CPIC	25 (89)	19 (95)	6 (75)
DWPG	2 (7)	0 (0)	2 (25)
Recommendation from a laboratory report	1 (4)	1 (5)	0 (0)
CDS for result interpretation and recommendations, n (%) ^a			
Interruptive (i.e., pop-up) alert in the EHR	16 (57)	13 (65)	3 (38)
Passive CDS (e.g., consultation notes, <i>DPYD</i> result displayed within fluoropyrimidine order field)	15 (54)	14 (70)	1 (13)
Lab portal that provides <i>DPYD</i> result interpretation and recommendations	4 (14)	2 (10)	2 (25)
No CDS	4 (14)	2 (10)	2 (25)
Other CDS tools ^b	3 (11)	2 (10)	1 (13)
Results returned to patients, n (%)			
Yes	21 (75)	16 (80)	5 (63)
No	6 (21)	3 (15)	3 (38)
Missing/Unknown	1 (4)	1 (5)	0 (0)
Methods of results return to patients, n (%) ^a			
Electronic copy accessed via EHR patient portal	17 (61)	15 (75)	2 (25)
Verbal return during provider visit	4 (14)	4 (20)	0 (0)
Physical paper copy/letter	3 (11)	2 (10)	1 (13)
Electronic copy accessed via lab portal	2 (7)	1 (5)	1 (13)
Other methods of test return ^e	1 (4)	0 (0)	1 (13)
Verbal return over the phone	1 (4)	1 (5)	0 (0)
Unknown	1 (4)	0 (0)	1 (13)

Abbreviations: CDS, clinical decision support, CPIC, clinical pharmacogenetics implementation consortium, DPWG, Dutch Pharmacogenetics Working Group; EHR, electronic health record.

^aSurvey question allowed for selection of multiple answers.

^bOne site stated interruptive alerts are built but not currently turned on, one site stated CDS tools are planned but undecided on exact tools, one site stated an external software is layered on top of the EHR for decision support.

^cOne site stated the laboratory report triggers a discrete entry into the problem list, one site stated an external software is layered on top of the EHR for return of results to clinicians.

^dOne site provides a medication safety card with a QR code to clinicians, one site stated the research laboratory directly contacts the oncologist.

^eOne site provides a medication safety card with a QR code to patients.

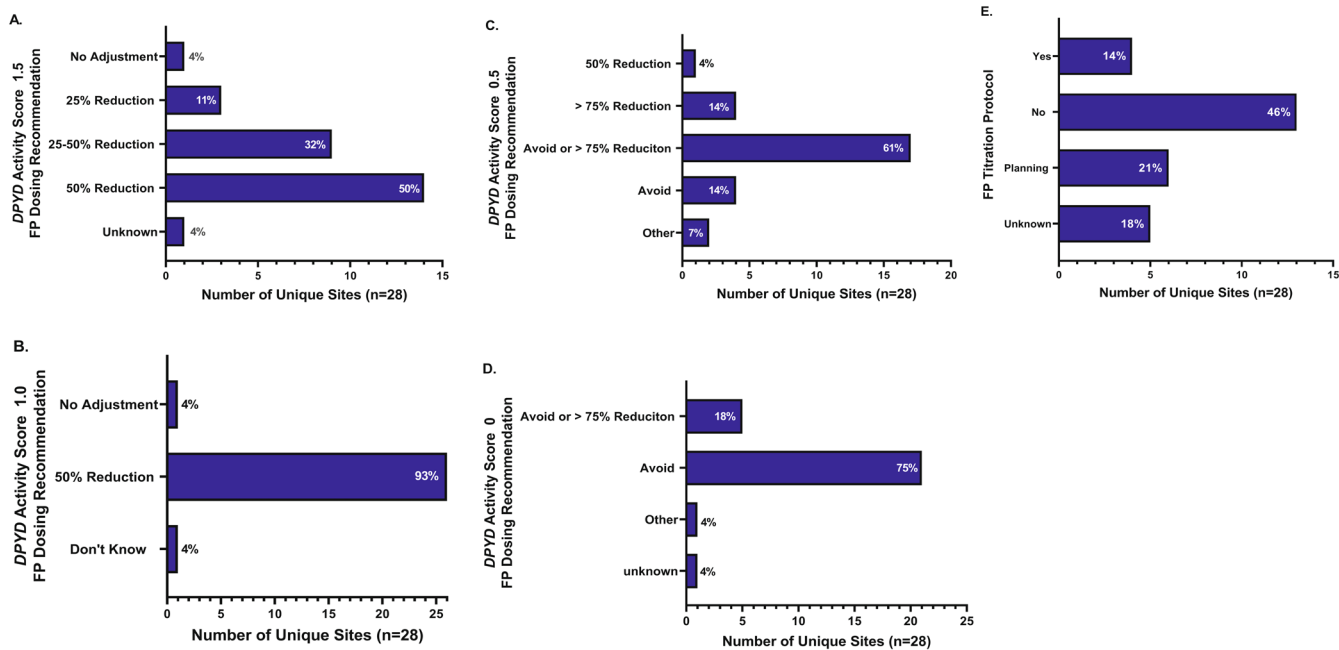


FIGURE 2 | *DPYD*-guided fluoropyrimidine (FP) dosing recommendations for (A) Activity score 1.5, (B) Activity Score 1, (C) Activity Score 0.5, (D) Activity Score 0. (E) Percent of sites with a FP titration protocol or planned protocol.

(Table S1). Most sites use, or plan to use, a mix of interruptive (57%) and/or passive (54%) CDS to supplement test interpretation and provide *DPYD*-guided therapeutic recommendations, though this was enriched for US sites (Table 4; Table S2).

Eighty-nine percent of sites used Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines to develop recommendations for *DPYD*-guided fluoropyrimidine dosing (Table 4) [9]. A higher percentage of non-US sites utilized the Dutch Pharmacogenetics Working Group (DPWG) which provides recommendations for tegafur [19]. For most *DPYD* activity scores, there was consistency in dosing recommendations across sites. Over 90% of sites recommended an initial 50% fluoropyrimidine dose reduction for a *DPYD* AS of 1.0, consistent with CPIC guidelines (Figure 2B). Similarly, most sites recommended > 75% dose reduction for *DPYD* AS 0.5 and 0, or to avoid fluoropyrimidines (Figure 2C,D). However, there were differences in dosing recommendations for a *DPYD* AS of 1.5, whereby sites reported no dose reduction, dose reduction of 50%, 25%, or a range of 25%–50% (Figure 2A). There was more variance among US sites compared to non-US sites, with over half of US sites recommending either a 25% fluoropyrimidine dose reduction or 25%–50% dose reduction, which is discordant with the current CPIC recommendation of a 50% dose reduction followed by titration to a higher dose if tolerated (Figure S5). A minority of sites indicated a fluoropyrimidine titration protocol was developed or planned to be developed (Figure 2E). A greater percentage of non-US sites (38%) indicated a titration protocol was already available compared to US sites (5%), though 30% of US sites indicated development of a titration protocol was planned (Figure S6). For sites with a titration protocol, or developing a protocol, respondents had the opportunity to provide a protocol description (Table S9). One site utilized a pharmacokinetic algorithm to guide fluoropyrimidine titration. No other site provided specific guidance for dose titrations beyond a general recommendation of considering fluoropyrimidine dose escalation if fluoropyrimidine cycles 1 and 2 are tolerated.

A majority of sites (75%) indicated their implementation strategy, or planned strategy, involved the return of *DPYD* results directly to patients, primarily via an electronic copy accessible through an EHR patient portal (Table 4; Table S2). The use of an EHR patient portal was more common among US sites (75%) compared to non-US sites (25%). Other methods for returning results to patients included verbal discussion during a provider visit (14%), paper copy given to the patient (11%), laboratory portal (7%), and phone-based communications (4%). Oncologists were reported to be the most frequently involved in returning results to patients, followed by a precision medicine or pharmacogenetics program and nurse or advanced practice provider (Table S1).

3.5 | Education Strategies

Numerous strategies were used across sites to provide clinicians education about *DPYD* testing. Personal communication was the most common method of *DPYD* education, with 61% of all sites using this approach (Table 5; Table S2). Workshops/in-services and education embedded within the EHR were also common methods of education among US sites, but these methods were not utilized among non-US sites. Continuing education was used by both US and non-US sites, with this method used to a greater extent at non-US sites.

A minority of sites (14%) provided education to patients about inherited pyrimidine metabolism disorders that can be associated with *DPYD* variants (Table 5). Of these sites, the timing of the education was mixed between pretest or at the time *DPYD* results were returned. Three sites indicated that patients who are found to carry *DPYD* variants are referred to Clinical Genetics, and one site indicated all patients undergoing *DPYD* testing are referred to Clinical Genetics. The specific types of education documents and content provided at the time of returning results were not a focus of this survey.

TABLE 5 | Education strategies.

Provider education for <i>DPYD</i> testing, n (%)^a	All (n = 28)	US (n = 20)	Non-US (n = 8)
Personal (e.g., email) communication or education	17 (61)	13 (65)	4 (50)
Workshops/in-services	11 (39)	11 (55)	0 (0)
Embedded links through EHR	10 (36)	10 (50)	0 (0)
Grand rounds	5 (18)	4 (20)	1 (13)
Continuing education	5 (18)	2 (10)	3 (38)
Website	4 (14)	3 (15)	1 (13)
No education	4 (14)	3 (15)	1 (13)
Unknown	2 (7)	1 (5)	1 (13)
Patient education			
Provide information about inherited pyrimidine metabolism disorders to patients, n (%)	All (n = 28)	US (n = 20)	Non-US (n = 8)
No	18 (64)	13 (65)	5 (63)
Unknown/missing	6 (21)	5 (25)	1 (13)
Yes	4 (14)	2 (10)	2 (25)
How is information about inherited pyrimidine metabolism disorders provided to patients, n (%)^a	All (n = 4)	US (n = 2)	Non-US (n = 2)
Verbally by a clinician	3 (11)	1 (5)	2 (25)
Other ^b	2 (7)	2 (10)	0 (0)
A patient education handout	1 (4)	1 (5)	0 (0)
When is information about inherited pyrimidine metabolism disorders provided to patients, n (%)	All (n = 4)	US (n = 2)	Non-US (n = 2)
Prior to testing	1 (25)	0 (0)	1 (50)
With result return	1 (25)	0 (0)	1 (50)
Both	1 (25)	1 (50)	0 (0)
Other ^c	1 (25)	1 (50)	0 (0)
Refer to clinical genetics (e.g., genetic counselor) when <i>DPYD</i> testing is performed for inherited pyrimidine metabolism disorders and/or cascade testing, n (%)	All (n = 28)	US (n = 20)	Non-US (n = 8)
No	15 (54)	12 (60)	3 (38)
Do not know/missing	7 (25)	6 (30)	1 (13)
Only patients who carry a <i>DPYD</i> variant	3 (11)	1 (5)	2 (25)
Institution does not have Clinical Genetics	2 (7)	0 (0)	2 (25)
All patients undergoing <i>DPYD</i> testing are referred	1 (4)	1 (5)	0 (0)

^aSurvey question allowed for selection of multiple answers.

^bTwo sites indicated it is variable dependent on provider.

^cOne site indicated it is variable dependent on provider.

4 | Discussion

This study reports findings from a global survey examining *DPYD* implementation with perspectives from countries not captured by previous surveys [26, 30, 35–37]. There was significant heterogeneity in how *DPYD* testing was implemented across survey respondents. Over 80% of sites indicated that they

employed a preemptive testing approach before fluoropyrimidine administration, but the timing of test ordering was variable. While all sites had created infrastructure to support testing, 70% indicated workflows were dependent on a clinician remembering to order the test. This may be due to strategies such as order sets not automatically ordering *DPYD* testing but rather serving as a tool to streamline testing, in which case clinicians still

have to remember to initiate the order set. Approximately half of sites indicated that *DPYD* testing was implemented in select clinics. Heterogeneity in *DPYD* implementation strategies may potentially be due to implementing clinic by clinic, where each clinic may prefer certain workflows rather than an institution-wide approach.

Our findings showed that penetrance of *DPYD* testing was low (<25%) among most sites, even though infrastructure had been developed to support testing. Our findings are similar to a previous US survey that reported only one-third of sites ordered *DPYD* testing for all fluoropyrimidine treated patients [30]. Results from our study suggest there is a need to further determine why penetrance was low and identify solutions to increase testing rates. Only a minority of sites (16%) in our study that had already implemented *DPYD* testing employed interruptive CDS to prompt testing. A recent study reported that testing rates increased from 9% to 96% after implementation of a preemptive strategy that included CDS to prompt *DPYD* testing [38]. Concerns about alert fatigue may impact implementation infrastructure decision-making, highlighting the need for optimal workflows that promote automated *DPYD* testing while avoiding alert fatigue [39–41]. Additional solutions will be needed for sites with limited EHR resources.

Only two sites reported *DPYD* testing rates of over 75% for patients planned to receive a fluoropyrimidine. Interestingly, those two sites depended on clinicians to remember test ordering. One site was in Europe, potentially highlighting the role national regulatory policies have on clinician acceptance of *DPYD* testing. Surveys from Europe and the United Kingdom reported a substantial increase in testing rates following national regulatory agencies recommending testing [26, 36]. In a survey conducted in the United Kingdom, over 90% of respondents reported *DPYD* testing was performed on all patients prior to receiving a fluoropyrimidine with uptake attributed to national regulatory guidance [36]. At the time that our survey was conducted, the US Food and Drug Administration (FDA) had recently updated guidance stating to consider *DPYD* testing prior to fluoropyrimidine therapy [13]. After our survey was administered, the FDA and National Comprehensive Cancer Network (NCCN) colorectal, rectal, anal, and small bowel cancers guidelines updated their guidance to recommend *DPYD* testing prior to fluoropyrimidine therapy [42]. Based on observations in Europe, where testing significantly increased following similar recommendations by the European Medicines Agency, the FDA and NCCN statements recommending *DPYD* testing are expected to increase penetrance in the US.

Among sites dependent on insurance billing to support *DPYD* testing, reimbursement rates may also impact testing penetrance. Improvements in test reimbursement rates were noted in Europe after national regulatory agencies recommended testing [26]. FDA and NCCN statements to consider *DPYD* testing may help support increased reimbursement rates, particularly in the US. *DPYD* reimbursement rates in the US may also increase due to recent passage of state biomarker testing bills that expand insurance coverage [43].

While our survey was administered before the publication of the AMP *DPYD* guideline that identified a minimum set

of variants to include in clinical assays, referred to as Tier 1 variants [12], most sites were already testing for the majority of *DPYD* Tier 1 variants. This is also consistent with EMA recommendations. Exceptions regarding the AMP Tier 1 alleles included *DPYD* c.868A>G and c.2279C>T, with a limited number of sites testing for these variants. Interestingly, 29% of sites tested for *DPYD**10 which is currently not listed as an AMP Tier 1 or 2 variant. A recent study reported that, in contrast to what has been assumed, there is not complete linkage disequilibrium for the *DPYD* HapB3 haplotype consisting of the benign c.1236G>A tag and the causal c.1129-5923C>G variant [44]. Of the sites testing for *DPYD* HapB3, three tested for the *DPYD* c.1236G>A tag only, which in rare instances could result in a patient with actual *DPYD* normal metabolizer status called an intermediate or poor metabolizer, resulting in fluoropyrimidine under-exposure or avoidance. One site indicated HapB3 variant selection may be reevaluated. This highlights the need for periodically reviewing the content of testing panels to keep abreast of emerging clinically important alleles and any updates to AMP recommendations to ensure equitable coverage of *DPYD* variants.

Only one-third of respondents indicated >75% of *DPYD* results were returned before fluoropyrimidine administration. There were no apparent associations between *DPYD* testing workflows or test turnaround time and high percent (>75%) of results returned before a fluoropyrimidine was administered. Though, ≥50% of results were returned before fluoropyrimidine administration for all sites that integrated *DPYD* test ordering into clinical workflows. Sites with high percent of *DPYD* results returned before fluoropyrimidine administration might have scheduled initial fluoropyrimidine administration based on return of results, though this survey did not assess factors that may influence timing of when results are returned and administration of a fluoropyrimidine. Furthermore, our survey did not assess time between *DPYD* test ordering and specimen collection. Any delays with specimen collection after test ordering would delay return of results. Our findings indicate there is a need for more efficient pre-test workflows, such as collaborative efforts for timely *DPYD* test ordering, specimen collection, and scheduling of chemotherapy administration, to ensure *DPYD* results are returned before the start of fluoropyrimidine therapy to help mitigate severe toxicities. Our results also highlight the importance of closely monitoring implementation metrics, especially early on, to refine workflows and processes as needed to ensure results are obtained prior to the start of therapy [45].

Over 80% of sites returned results in the EHR as discrete data and used a combination of interruptive and passive EHR-based CDS to deliver dosing recommendations based on CPIC guidelines. US sites used EHR CDS to a greater extent than non-US sites, which highlights a potential need for diverse methods of providing *DPYD*-guided dosing recommendations globally. While sites reported utilizing CPIC guidelines to guide implementation efforts, there was wide variation in fluoropyrimidine dosing recommendations for *DPYD* AS 1.5, defined as harboring one normal function allele in combination with select decreased-function *DPYD* variants [9]. CPIC guidelines currently recommend a 50% dose reduction for a *DPYD* AS of 1.5, but there are emerging data suggesting that

a 25% fluoropyrimidine dose reduction may be sufficient for patients who harbor select decreased-function variants (e.g., HapB3 haplotype) to prevent severe toxicities, with dose reductions larger than 25% potentially affecting efficacy [24]. CPIC also recommends titration to a higher returned before a fluoropyrimidine dose based on tolerance [9]. Few sites reported the use of a titration protocol, consistent with prior studies demonstrating that limited patients undergo titration to optimize dose exposure [14, 24]. Future implementation strategies should consider incorporating titration protocols to maximize the balance between mitigation of toxicities and fluoropyrimidine effectiveness.

With evidence continually evolving regarding which *DPYD* variants to test and the associated therapeutic recommendations, it may be beneficial for health care institutions to establish a precision medicine or pharmacogenetics team to guide, monitor, and adapt *DPYD* implementation strategies. Indeed, there have been calls in oncology to establish multidisciplinary teams with a focus on the interpretation and application of biomarker test results [46, 47]. Over half of respondents indicated that a precision medicine or pharmacogenetic program was instrumental in championing *DPYD* testing, with about half of sites also indicating such programs were vital for leading implementation efforts. Oncologists, pharmacists, nurses, molecular pathologists, and genetic counselors were all identified as having important roles in *DPYD* implementation strategies, demonstrating the importance of engaging a multidisciplinary group of clinicians when implementing *DPYD* into patient care.

There are limitations to this study which may influence the generalizability of results. First, the survey was disseminated only to members of the PGRN Implementation Working Group, and while we aimed for a global representation, most of the respondents were from the US. However, non-US sites were largely distinct from previous surveys conducted in the UK [36], the Netherlands [35], and other European countries [26], providing additional global perspectives on *DPYD* implementation strategies. In contrast to prior studies in Europe, the vast majority of sites included in this survey resided within countries where national regulatory agencies do not recommend *DPYD* testing. Most respondents were from academic institutions, and survey results may not fully represent implementation strategies in community settings, especially those with more limited resources. Some sites might have provided estimates rather than actual counts of *DPYD* testing rates and return of results before fluoropyrimidine administration, which could result in underestimation or overestimation of findings. Inherent with any survey, particularly globally, respondents may not have understood the context of every question. Nevertheless, the survey was reviewed by international PGRN members before dissemination to help ensure clarity.

5 | Conclusions and Future Directions

Our survey provided additional insights into the international landscape of *DPYD* testing that identified common practices that may be applicable worldwide for guiding implementation strategies. Although numerous strategies were used to guide

DPYD test ordering, 70% of sites reported dependence on clinicians to remember test ordering. Dependence on clinicians to remember *DPYD* test ordering, along with 96% of sites residing in countries that lacked national regulatory policies that strongly recommended testing, may have contributed to low penetrance of testing. Additionally, only one-third of respondents indicated greater than 75% of *DPYD* results were returned before fluoropyrimidine administration, highlighting the need for more efficient pre-test workflows. In future studies, employing more robust qualitative or mixed-methods implementation science approaches may help identify factors that support successful implementation [48, 49]. Safe and effective fluoropyrimidine use can be achieved by developing efficient implementation strategies that ensure all patients undergo *DPYD* testing with results returned before start of therapy.

Author Contributions

All authors designed the research and wrote the manuscript. N.E.R., J.D.D., K.G., and J.K.H. performed the research. J.K.H. and N.E.R. analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1. Data S2.**