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Province-Wide Implementation of Pre-Therapeutic DPYD Genotyping to Prevent Severe Fluoropyrimidine Toxicity in British Columbia

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ABSTRACT

Toxic responses to fluoropyrimidines frequently stem from variations in DPYD, the gene coding for dihydropyrimidine dehydrogenase (DPD). Identifying DPYD variants allows clinicians to individualize treatment to lower the risk of fluoropyrimidine-associated adverse effects while still achieving effective drug exposure. A multiplex qPCR test was created in-house to detect six DPYD polymorphisms. This assay was offered prospectively to every patient beginning fluoropyrimidine therapy at the BC Cancer Centre in Vancouver and subsequently throughout British Columbia, Canada, and was also used retrospectively for individuals suspected of having toxicity. Dose modifications were implemented for carriers of deleterious variants. Rates of toxicity during the initial three treatment cycles were assessed in carriers versus non-carriers. After an introductory rollout period, the test became accessible across the province.

Over a 9-month interval, 186 individuals underwent testing, with 14 identified as heterozygous for a variant. Toxicity linked to fluoropyrimidines occurred more frequently among carriers. Among 127 non-carriers who completed therapy, 18 (14%) developed grade ≥3 adverse events (CTCAE v5.0). Notably, 22% of the heterozygous patients (3 individuals) exhibited severe toxicity despite dose reductions based on DPYD. In one case, presenting with marked thrombocytopenia within the first week, early genotyping likely prevented a fatal reaction. When variant carriers tolerated initial reduced dosing, a subsequent 25% dose escalation triggered treatment cessation. Consequently, guidance was issued recommending that clinicians increase doses by only 10% after two toxicity-free cycles in this population. Dose adjustments derived from DPYD genotyping were practical and effective for limiting major toxicity in carriers. Nonetheless, some carriers experienced significant fluoropyrimidine toxicity even after reduction, reinforcing the need to strictly follow dosing guidelines. After the pilot period, DPYD testing was implemented province-wide in British Columbia.

Keywords: Adverse drug reactions, Implementation, DPYD, Fluoropyrimidine toxicity, Pharmacogenetics

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Introduction

Roughly two million cancer patients globally receive fluoropyrimidines each year. This class includes 5-fluorouracil (5-FU) and its prodrug capecitabine, which is metabolized into 5-FU [1, 2]. These drugs serve as foundational agents in oncology, used in both adjuvant and palliative settings for many solid malignancies such as colorectal, head and neck, gastric, pancreatic, and breast cancers. However, 10%–40% of patients develop severe treatment-related adverse effects, causing hospitalization, treatment interruption, or, in about 1%, death [3–6]. Approximately 10% experience severe reactions within their first three cycles and must discontinue therapy [7]. Frequent toxicities include diarrhea, nausea, vomiting, mucositis, myelosuppression, and hand–foot syndrome (HFS) [8].

A major and well-documented contributor to fluoropyrimidine intolerance is reduced activity of DPD, the primary enzyme responsible for inactivating 5-FU, most often due to polymorphisms in DPYD. Variation in DPD activity leads to markedly different systemic drug exposures, placing some individuals at considerably higher risk.

Numerous retrospective and prospective studies demonstrate that patients with partial DPD deficiency who receive standard doses face a substantially elevated likelihood of serious toxicity [9–15]. The variant most thoroughly characterized is DPYD 2A (c.1905+1G>A), which abolishes enzyme function. Roughly 1.6% of people of European descent are heterozygous for this allele and exhibit about a 50% decrease in DPD activity compared with those carrying two functional copies [6, 16]. Three additional variants—DPYD 13 (c.1679T>G), and the reduced-function alleles c.2846A>T and c.1236G>A (HapB3)—are also associated with markedly increased toxicity [6, 17]. Collectively, these four clinically important alleles appear in 3%–8% of individuals of European ancestry. Current expert guidelines recommend screening for all four [6, 18, 19].

A large number of additional DPYD alterations that influence DPD activity in cell-based assays are extraordinarily uncommon and therefore have not appeared in major population datasets [6, 20]. Because Vancouver includes patients from many ancestral backgrounds, two extra variants were evaluated. Individuals with African ancestry may carry c.557A>G—found in roughly 3%, which can heighten susceptibility to fluoropyrimidine toxicity, while about 1% of people of South Asian descent possess c.2279C>T, another reduced-function allele [20–22].

A prospective investigation involving 2,038 participants screened for DPYD 2A revealed that reducing the starting fluoropyrimidine dose by 50% in carriers decreased the rate of severe toxicity from 73% to 28%, approximating the 23% observed in non-carriers who received full doses [6]. A separate large-scale trial by Henricks *et al*. focused on the four "European" DPYD variants and found that halving the initial dose for heterozygous c.1905+1G>A patients lowered severe toxicity from 77% to 18% [17]. Their results also demonstrated that cutting the dose by only 25% for those with c.1236G>A or c.2846A>T did not sufficiently reduce risk, as severe toxicity still occurred in 39% and 47% of these patients, respectively. As a result, CPIC updated its guidance to recommend a 50% starting-dose reduction for all patients with either loss-of-function or reduced-function alleles [6].

Crucially, these clinical studies showed that lowering doses for variant carriers did not compromise drug exposure. Pharmacokinetic comparisons indicated that heterozygous carriers given reduced amounts of capecitabine or 5-FU achieved systemic concentrations similar to non-carriers treated at standard doses [17]. Retrospective assessments further demonstrate that carriers can face up to an 88% higher probability of grade ≥3 toxicity [23, 24]. Because variant frequencies are not negligible, pre-emptive genotyping can identify many patients at elevated risk [6]. Prospective evidence shows that genotype-adjusted dosing reduces toxicity without impairing survival outcomes [25], and equivalency of fluorouracil exposure has been documented across different regimens when dosing is genotype-guided [16, 17, 25].

Despite this, North American practice has not yet adopted routine pre-treatment DPYD screening, although a few implementation efforts have been reported [26–28]. NCCN, ASCO, and the FDA currently stop short of recommending universal testing. At the same time, several international authorities take the opposite stance. Regulatory agencies in Europe—including the EMA, France's national drug-safety authority, and the UK's MHRA—have each endorsed guidelines promoting advanced assessment of DPD activity before fluoropyrimidine administration [29–32]. Recent expert discussions highlight the inconsistency within North American guidance [28, 33, 34]. Although FDA labeling recognizes that people with DPD deficiency face a major risk of life-threatening toxicity, it merely states that patients who already know they are deficient should speak with their clinicians—a scenario that rarely occurs in practice. Specialists in oncology and pharmacotherapy have therefore urged NCCN, ASCO, and the FDA to adopt pre-treatment testing as standard care. It is noteworthy that the Dana-Farber Cancer Institute initiated a formal DPYD testing program in 2022 and that Oregon Health & Science University agreed to a USD $1M settlement after a patient fatality was attributed to unrecognized DPD deficiency.

Within Canada, approaches such as phenotyping or therapeutic drug monitoring (TDM) to measure DPD activity are not in routine use. Without prospective genotyping, clinicians cannot detect patients who require lower starting doses, leaving a substantial portion of severe toxicity events preventable. Before this program, British Columbia did not offer systematic DPYD screening, so individuals at heightened risk of fluoropyrimidine toxicity frequently remained unidentified before treatment, increasing avoidable morbidity and mortality.

Materials and Methods

A clinical framework was established to support fluoropyrimidine dose selection informed by DPYD genotyping, using a panel of six variants **(Table 1)**. This framework was first put into operation at the BC Cancer Vancouver Centre in August 2022 and later became the basis for a province-wide adoption in May 2023. Its primary purpose was to reduce the incidence of serious drug-related toxicities by personalizing fluoropyrimidine dosing according

to DPYD status. A further objective was to collect forward-looking data to refine dosing rules, especially for alleles more common among individuals with non-European backgrounds (c.557A>G, c.2279C>T).

Table 2. DPYD alleles included in the testing panel, with activity scores and frequency data derived from Amstutz *et al*., 2018.

DPYD Variant	Allelic Effect	Activity Rating (Amstutz *et al.*, 2018)	Variant Prevalence by Ancestry	European	Afro-Caribbean	Sub-Saharan African	East Asian	South Asian	Latino
c.1905+1G>A (DPYD*2A)	Loss-of-function	0	Frequency	0.008	0.003	0.000	0.000	0.005	0.001
c.1679T>G (DPYD*13)	Inactive allele	0	Frequency	0.001	0.000	0.000	0.000	0.000	0.000
c.2846A>T	Partially functional	0.5	Frequency	0.004	0.003	0.000	0.000	0.001	0.002
c.1236G>A (HapB3)	Diminished activity	0.5	Frequency	0.024	0.003	0.000	0.000	0.020	0.006
c.557A>G	Reduced enzyme action	0.5	Frequency	0.000	0.012	0.026	0.000	0.000	0.001
c.2279C>T	Decreased activity	0.5	Frequency	0.000	0.000	0.000	0.000	0.006	0.000

Study design and participants

This project aimed to embed DPYD testing directly into routine oncology care and to document prospective findings during the first 9 months after launch. It was organized as an observational study at the BC Cancer Vancouver Centre. Adults aged 18 years or older who were preparing to begin therapy containing fluoropyrimidines were eligible for participation (anticipated enrolment: 20–30 participants each month), with referrals handled by their treating oncologists.

Ethics approval was granted in June 2022, and prospective DPYD analysis became accessible to patients at the Vancouver site toward the end of August 2022. Written informed consent was required for participation. Additional consent allowed biobanking of biospecimens to enable later exome or genome sequencing aimed at discovering rare alleles. Testing expenses were fully covered by the provincial health program.

Procedures

A step-by-step workflow was prepared to define responsibilities across the clinical and laboratory teams, as well as the research staff **(Figure 1)**.

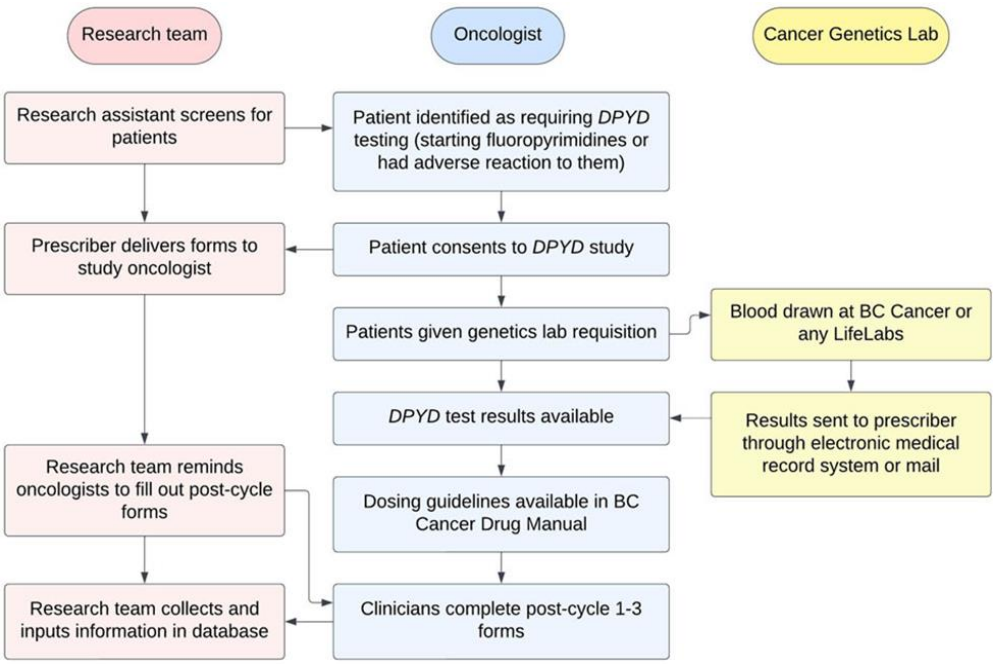

Figure 1. Workflow summarizing the rollout of DPYD testing in British Columbia.

Before starting chemotherapy, participants provided consent and underwent testing for the six DPYD variants: DPYD2A, DPYD13, c.2846A>T, c.1236G>A, c.557A>G, and c.2279C>T **(Table 1)**. When agreeable, patients documented their ancestry by identifying the countries of birth of their parents and grandparents; if unavailable, a more general regional description (e.g., "European") was accepted. A paper requisition signed by the patient's oncologist was issued, and blood samples were collected either centrally at BC Cancer or at community collection centres around the province. Samples were then forwarded, as per routine clinical protocols, to the Cancer Genetics and Genomics Laboratory for analysis and reporting.

Genomic DNA (gDNA) was isolated from 150 µL of buffy coat using the Maxwell RSC Buffy Coat DNA Kit and the Maxwell RSC platform (Promega, Wisconsin, United States). Variant analysis relied on quantitative PCR performed on a QuantStudio 7 Pro instrument (ThermoFisher, Massachusetts, United States). Each multiplex reaction included 10 ng of gDNA measured by Nanodrop (ThermoFisher). Custom probe and primer sets (sequences available on request) were engineered to interrogate all six DPYD variants using three multiplex reactions. Each run incorporated DPYD Multiplex Set controls (SensID, Rostock, Germany), as well as laboratory-prepared controls generated from gBlocks (IDT, Iowa, United States) and cell lines, along with a no-template control. These controls captured all genotype categories—wild-type, heterozygous, and homozygous—and were used to assign patient genotypes with the Genotyping module in QuantStudio Real-time PCR Software v1.7.2 (ThermoFisher). The median reporting time was 6 days, after which results were uploaded directly into the patient's electronic medical record.

The clinical report provided each individual's DPYD genotype together with a projected activity score (examples are shown in the Supplementary Material). Because the panel only assessed six DPYD variants, the score was explicitly described as an estimate; individuals who harbour uncommon, untested loss-of-function alleles would not have their true enzyme activity reflected. A dosing reference derived from CPIC recommendations is posted online in both the Cancer Drug Manual© Appendix and the Drug Index for capecitabine and 5-FU **(Table 2)**. In this dosing framework, a reduced-function allele contributes 0.5 activity units and a non-functional allele contributes 0, with scores summed across alleles [6]. Based on this table, intermediate metabolizers with a total activity score of 1.0 were started at 50% of the usual dose. Clinicians ultimately extended this 50% starting reduction to those with an activity score of 1.5 as well, given prior evidence showing increased toxicity and higher metabolite accumulation with only a 25% dose cut [17] and because applying a single cut-off streamlined clinical use **(Table 2)**.

Table 2. Dose-adjustment guidance for capecitabine and 5-fluorouracil by DPYD activity score. CPIC guideline links are provided, and the updated recommendation that individuals homozygous for c.2846A>T may need more than a 50% dose decrease is highlighted.

Estimated Activity Score	Genotypic Pattern	Expected DPYD Phenotype	Guidance for Fluoropyrimidine Dosing
0	Two non-functional alleles (homozygous or compound heterozygous)	Poor metabolizer	Avoid treatment entirely
0.5	Combination of one non-functional allele and one reduced-function allele	—	Use is generally discouraged. If no alternative therapy is feasible, begin with a markedly lowered dose (minimum 75% reduction) and monitor drug levels promptly.
1.0	Heterozygous for a non-functional allele	Intermediate metabolizer	Initiate therapy at half the typical starting dose. Adjust subsequent doses according to clinical evaluation.
	Homozygous for a reduced-function allele*		
1.5	Carrier of a single reduced-function allele	—	Begin treatment with a 25–50% dose decrease. Modify dosing later based on clinical assessment.
2.0	No detected variants	Normal metabolizer	No dose modification recommended

Clinical and demographic information were stored within a REDCap database. Variables collected included cancer diagnosis, comorbid illnesses, routine laboratory data, DPYD results, treatment details, and toxicity

outcomes. Toxicities captured included neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, hand–foot syndrome, mucositis, chest pain, and any additional treatment-related events. For the first three treatment cycles, oncologists documented toxicities using standardized forms containing grading criteria from CTCAE v5.0 [35]. These were completed during post-cycle visits, during which patients were systematically asked about each symptom. Hospital admissions, unscheduled medical visits, general practitioner or urgent care consultations, and calls to the BC Cancer nursing triage line attributed to fluoropyrimidine toxicity were also logged.

Outcomes

The central outcome measure was the proportion of patients carrying DPYD variants who experienced severe toxicity (CTCAE grade ≥3) compared with those without such variants. Additional outcomes focused on implementation metrics, such as the proportion of patients whose dosing was altered according to the genotype-informed recommendation and the proportion of test results finalized before treatment began. Testing uptake was evaluated by comparing the number of patients tested and enrolled against the number of new individuals initiating fluoropyrimidine-based therapy. Exploratory analyses examined fluoropyrimidine dose intensity in variant carriers versus non-carriers and evaluated variant frequencies and toxicity patterns across self-reported ancestry groups. Relative dose intensity was defined as the administered dose divided by the standard regimen dose.

Statistics

Descriptive statistics were used to contrast baseline variables between participants with and without the tested DPYD variants. Distribution of age was evaluated using the Shapiro–Wilk test ($p < 0.05$), leading to the use of nonparametric approaches. Age differences between groups were examined with the Mann–Whitney U test. Dichotomous variables were compared using Fisher's exact test. A p-value < 0.05 was regarded as statistically significant.

Results and Discussion

From September 2022 to May 2023, DPYD testing was completed for 186 individuals **(Table 3)**. The most frequent cancer types in the cohort were colorectal (n = 80; 52%), breast (n = 21; 14%), and pancreatic (n = 18; 12%). Self-identified ancestry most commonly included European (n = 84; 55%) and East Asian (n = 26; 17%) backgrounds. Fourteen participants (8%) were heterozygous carriers of DPYD variant alleles. Comparisons between variant carriers and non-carriers showed no meaningful differences in age, sex, tumour category, tumour stage, or treatment regimen.

Table 3. Characteristics of the 186 patients undergoing DPYD testing for fluoropyrimidine-based therapy. Age comparisons used Mann–Whitney U tests; sex, ancestry, tumour type, and regimen type were assessed using Fisher's exact test. Significance was defined as $p < 0.05$.

	Total (n = 186)	Individuals with variants (n = 14)	Individuals without variants (n = 172)	p-value
Sex				
Male	87 (47%)	7 (50%)	82 (48%)	1.00
Age				
Median (IQR)	63 (56–73)	66 (54–74)	63 (56–73)	0.63
Self-reported ancestry[a]	—	—	—	0.14
European	113 (61%)	13 (93%)	100 (55%)	—
African	2 (1%)	1 (7%)	1 (1%)	—
East Asian	31 (17%)	0 (0%)	31 (18%)	—
South Asian	14 (8%)	0 (0%)	14 (8%)	—
Indigenous	5 (3%)	0 (0%)	5 (3%)	—
Hispanic	4 (2%)	0 (0%)	4 (2%)	—
Mixed heritage (European/East Asian/African)	6 (3%)	0 (0%)	6 (3%)	—

Chose not to disclose	11 (6%)	0 (0%)	11 (6%)	—
Tumor category	—	—	—	0.52
Colorectal	98 (53%)	6 (43%)	92 (53%)	—
Gastric	9 (5%)	0 (0%)	9 (5%)	—
Esophageal	6 (3%)	1 (7%)	5 (3%)	—
Pancreatic	23 (12%)	2 (14%)	21 (12%)	—
Anal	9 (5%)	2 (14%)	7 (4%)	—
Biliary tract	13 (7%)	1 (7%)	12 (7%)	—
Breast	22 (12%)	2 (14%)	20 (12%)	—
Other (liver, gallbladder, unknown primary)	6 (3%)	0 (0%)	6 (3%)	—
Cancer stage	—	—	—	0.67
I	5 (3%)	0 (0%)	5 (3%)	—
II	27 (15%)	3 (21%)	24 (14%)	—
III	85 (47%)	5 (36%)	80 (47%)	—
IV	69 (37%)	6 (43%)	63 (37%)	—
Treatment protocol	—	—	—	0.88
5-FU–based combination regimen	59 (32%)	4 (29%)	55 (32%)	—
Capecitabine alone	44 (24%)	3 (21%)	41 (24%)	—
Capecitabine + platinum drug	45 (24%)	3 (21%)	42 (24%)	—
Capecitabine + additional anticancer agents	4 (2%)	0 (0%)	4 (2%)	—
Capecitabine + radiotherapy	34 (18%)	4 (29%)	30 (17%)	—
DPYD genotype classification				
No detectable variants	172 (92%)	0 (0%)	172 (100%)	—
DPYD*2A heterozygous	3 (2%)	3 (21%)	0 (0%)	—
DPYD*13 heterozygous	1 (1%)	1 (7%)	0 (0%)	—
c.1236G>A heterozygous	7 (4%)	7 (50%)	0 (0%)	—
c.2846A>T heterozygous	2 (1%)	2 (14%)	0 (0%)	—
c.557A>G heterozygous	1 (1%)	1 (7%)	0 (0%)	—
c.2279C>T heterozygous	0 (0%)	0 (0%)	0 (0%)	—

a This investigation did not have sufficient statistical power to evaluate differences across ancestry groups.

Of the 14 DPYD variants detected in the cohort, four were recognized only after patients had already stopped fluoropyrimidine therapy due to toxicity **(Figure 2)**. Among the remaining 10 carriers identified prospectively, three learned of their results after beginning treatment. One individual completed the first cycle at a full dose without complications, but fluoropyrimidines were discontinued, as the clinician determined the expected benefit was low and the potential for toxicity in future cycles was high. The two other patients had their doses adjusted in the second cycle according to guideline advice, and one of them still experienced severe toxicity (CTCAE grade 3). Because these two individuals received prompt dose modifications, they were categorized as dose-reduced DPYD variant carriers in the analysis **(Table 4)**. Seven carriers obtained their pharmacogenetic results before starting therapy and therefore received an initial 50% dose reduction in cycle 1.

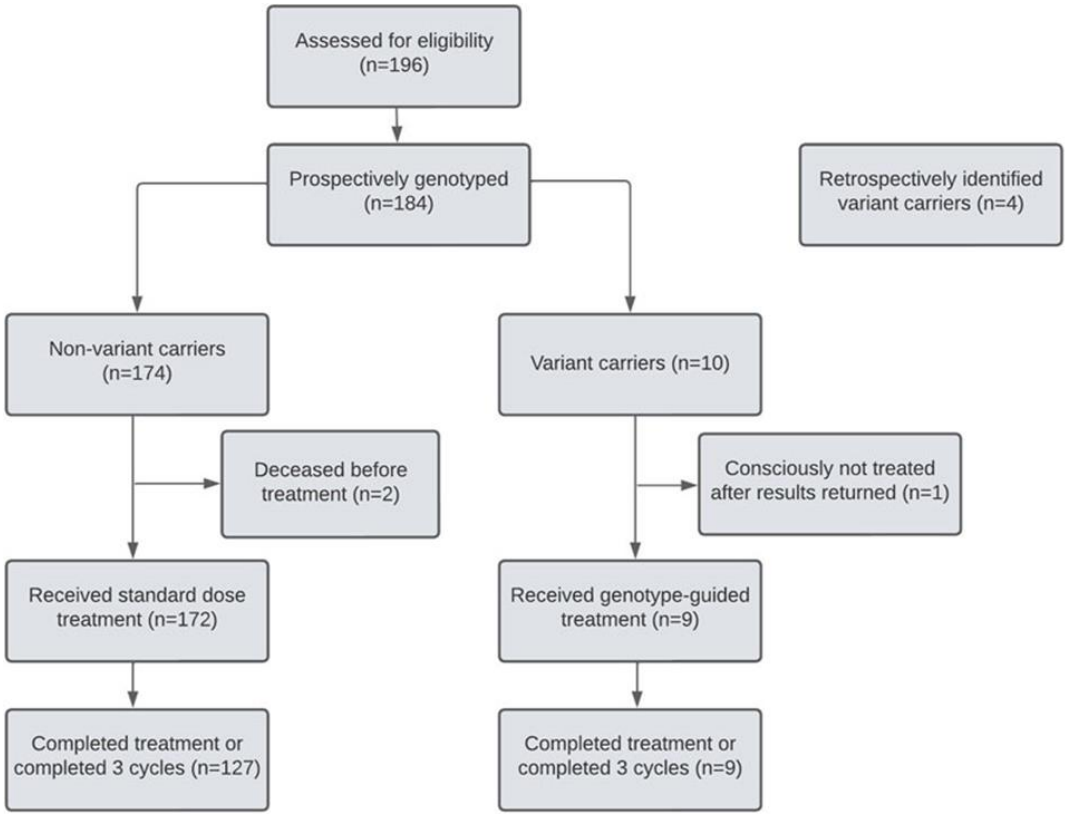

Figure 2. CONSORT diagram.

Table 4. Toxicity outcomes within the first three treatment cycles. Fisher's exact tests determined significance. A p-value < 0.05 was considered significant.

	DPYD Variant Carriers with Dose Reduction (n = 9)	Patients Without Variants (n = 127)	p-value
Chemotherapy completion (up to 3 cycles)			
Any grade 3 toxicity	2 (22%)	18 (14%)	0.62
Gastrointestinal (GI) grade 3	0 (0%)	12 (8%)	1.00
Hand–foot syndrome (HFS) grade 3	1 (11%)	0 (0%)	0.066
Hematologic grade 3	1 (11%)	6 (5%)	0.39
Any grade 2 toxicity	3 (33%)	34 (27%)	0.70
GI grade 2	2 (22%)	23 (18%)	0.67
HFS grade 2	1 (11%)	2 (2%)	0.19
Hematologic grade 2	1 (11%)	9 (7%)	0.51
Median cycle of first grade 3 event (IQR)	1.5	1.5 (1–2)	—
Hospitalizations due to fluoropyrimidine toxicity	1 (11%)	6 (5%)	0.39

During the first three cycles, toxicity profiles were evaluated in non-variant patients and in carriers whose therapy was adjusted based on DPYD results **(Table 4)**. All nine dose-reduced variant carriers completed three cycles—along with 127 (74%) of the 178 non-variant individuals, or completed treatment before the third cycle **(Figure 2)**. The median relative dose intensity among variant carriers was 50% (IQR 45%–74.5%), whereas non-variant patients largely remained at full dosing, with a median relative dose intensity of 100% (IQR 92%–100%). Among the nine carriers receiving DPYD-guided dose reductions, two experienced severe fluoropyrimidine-related toxicity, compared with 14% of non-variant patients treated at standard doses **(Table 4)**. One (11%) dose-reduced carrier required hospitalization for treatment-related toxicity, compared with six (5%) among non-variant individuals.

Toxicity prevention with DPYD-guided dosing in variant carriers

Carriers whose variants were uncovered only after toxicity developed all suffered substantial adverse effects, prompting cessation of chemotherapy after a single full-dose cycle. One individual receiving full-dose capecitabine for metastatic breast cancer developed severe oral mucositis, causing major pain and restricted oral intake, along with CTCAE grade 3 diarrhea (>7 stools/day). Additional findings included grade 2 HFS and hospitalization following an aortic thrombosis. Another patient receiving capecitabine at full dose for colorectal cancer also developed prolonged CTCAE grade 3 diarrhea and required admission.

Seven of the nine prospectively identified carriers tolerated fluoropyrimidines well, completing treatment while experiencing only grade 1 events. One patient, treated with capecitabine plus radiotherapy for stage IIIA anal squamous cell carcinoma, developed CTCAE grade 3 thrombocytopenia despite a 50% starting dose and normal renal function, leading to hospitalization. Platelets fell from 198 × 10^9/L to 35 × 10^9/L. After one week, therapy resumed at 25% of the full dose, and the cycle was completed without later severe effects. Another carrier (c.557A>G) with metastatic breast cancer began cycle 1 at full dose and developed diarrhea (four stools/day), CTCAE grade 2 mucositis, and grade 2 HFS with peeling and blister formation. Even after reducing the dose for cycle 2, the HFS worsened to grade 3, causing significant pain and ulceration; an additional dose reduction in cycle 3 led to improvement (grade 2).

Dose tolerance of DPYD variant carriers

Two carriers underwent dose escalation; one tolerated it, while the other developed significant toxicities. The first case involved a patient with metastatic pancreatic adenocarcinoma whose DPYD results became available during cycle 1. A 50% reduction was applied for cycle 2 without complications, and the dose was subsequently increased to 67% for cycle 3, resulting only in CTCAE grade 2 nausea that was alleviated with metoclopramide.

In contrast, the second escalation attempt was unsuccessful. This patient, treated with capecitabine and oxaliplatin for stage IV esophageal adenocarcinoma before DPYD testing existed, initially received 50% of the full dose because of renal dysfunction. Absence of toxicity in the first two cycles prompted escalation to 75% for cycle 3. The increased dose caused CTCAE grade 3 diarrhea (>7 stools/day) and CTCAE grade 2 HFS with swelling and blistering severe enough to interfere with daily living.

Implementation outcomes

Before each patient's first oncology visit, oncologists verified whether they met the criteria for enrollment. Of the 196 individuals evaluated, 12 ultimately did not receive fluoropyrimidine-based therapy and were therefore excluded **(Figure 2)**. No patient refused genotyping.

DPYD analysis was requested during the initial consultation. The turnaround time ranged 2 to 10 days, with a median of 6 days. Chemotherapy was typically arranged 2–3 weeks after the first visit, allowing 80% of patients to have their results available before cycle 1 began. Earlier in program implementation, chemotherapy was often initiated within 2–3 days of diagnosis. Because the laboratory processed tests on a weekly schedule, the workflow was revised so that DPYD testing was ordered concurrently with routine pre-chemotherapy bloodwork done prior to the first oncology appointment. This adjustment ensured that genotyping results would be ready before fluoropyrimidines were administered. In the final month of the year-long implementation, only 2 of 20 patients experienced a treatment postponement—up to one week—due to test processing time.

A dosing reference table was assembled to help clinicians interpret DPYD activity scores and apply the reductions recommended in guideline documents **(Table 2)**. Oncologists were directed to the BC Cancer Drug Manual, an online Provincial Health Services Authority resource, which includes drug monographs and standard patient education materials used before chemotherapy scheduling.

Carriers of DPYD variants are predisposed to severe fluoropyrimidine toxicity because their impaired metabolism leads to elevated systemic 5-fluorouracil levels [36]. Although this study did not include pharmacokinetic sampling, findings from other prospective DPYD-guided trials show that dose adjustments can normalize drug exposure in heterozygous carriers, allowing them to reach concentrations similar to non-carriers treated with full doses [16, 17]. Still, substantial inter-individual variation exists in capecitabine and metabolite exposure, suggesting cautious interpretation of pharmacokinetic data [12].

The DPYD-informed dosing strategy enabled 7 of 9 carriers to receive fluoropyrimidines with improved safety, likely averting severe dose-related toxicities. Previous literature reports >70% rates of severe toxicity among carriers treated with standard doses [12, 16]. In our cohort, 2 of 9 still developed grade 3 reactions. One notable

case involved a patient hospitalized 8 days after starting capecitabine: even with a 50% dose, the platelet count dropped 82% to 35 × 10^9/L. After reducing the dose further (>50% reduction), the patient completed adjuvant capecitabine with concurrent radiotherapy. For anal squamous cell carcinoma, this combined regimen is crucial to achieving a complete clinical response, documented in 89.7% of cases [37]. This experience strongly influenced oncologists' opinions on the necessity of pre-treatment DPYD genotyping. Initially, most clinicians doubted its value—mirroring US data where only 32% reported they would recommend routine testing [38]—but the severity of this toxicity persuaded them that genotyping likely prevented a life-threatening reaction. As a result, oncologists have become more inclined to follow recommended dose-reduction strategies, supported by reminders that carriers generally experience far higher toxic exposures than non-carriers.

Among non-variant carriers, 14% experienced severe toxicity, aligning with the expected 10%–30% range [7, 14, 39, 40]. Gastrointestinal events were most frequent (8%), followed by hematological complications (5%) **(Table 4)**, consistent with previously reported patterns [7]. Because DPYD variants are a major determinant of early-cycle toxicity [40], carriers not only faced a higher probability of adverse reactions but often developed multiple overlapping toxicities, increasing the chance of treatment interruption or cessation. The fact that 2 out of 9 still developed grade 3 toxicity in cycles 1–2, despite reduced dosing, further highlights the substantial vulnerability of carriers [40].

While guidelines recommend titrating doses upward after DPYD-guided dose reductions if patients show good tolerance [6], oncologists expressed uncertainty about how aggressively to escalate in carriers. One patient experienced nausea in cycle 3 after an increase from 50% → 67%, which was controlled with anti-emetics. Another patient—whose DPYD status was unknown during treatment—developed severe diarrhea when capecitabine was increased from 50% → 75%. Had the patient's carrier status been known, a smaller increment might have been chosen. A study evaluating tolerance-based escalation reported that 11 heterozygous carriers tolerated, on average, an 8.5% increase in capecitabine dose [41]. More evidence is required to guide safe dose escalation strategies. Considering the risk of severe reactions and the potential for discontinuation of therapy, the guidelines were adjusted to recommend 10% dose increases for carriers who complete two cycles at a reduced dose without toxicity.

The authors note that published evidence offers very limited guidance on how to escalate doses in DPYD variant carriers. Existing prospective trials focusing on DPYD-informed dose reductions did not specify the magnitude of upward dose adjustments [16, 17]. Henricks *et al*. reported that 5 of 11 attempted increases in carriers were not tolerated, necessitating renewed dose decreases or stopping treatment altogether. Although the actual escalation increments were not described, these observations highlight the need for a cautious and conservative approach to dose increases. Some studies have integrated TDM-based algorithms for 5-FU titration. For example, Kaldate *et al*. recommended increasing doses by no more than 30% per cycle when the AUC is below 8, aiming for an AUC target between 20 and 30 [42]. Comparable TDM frameworks for capecitabine have not been validated, and phase III research has shown that systemic concentrations of capecitabine and its metabolites are poor predictors of toxicity, leading investigators to advise against using TDM for this agent [43].

A further limitation of the present study was the lack of assessment of other individualized dosing strategies, such as phenotyping and TDM, to quantify DPD activity. When combined with genotyping, these approaches could identify additional patients susceptible to fluoropyrimidine-related harm. Evidence suggests that TDM can enhance both the consistency of 5-FU exposure and the overall safety profile [44]. It may also prevent sustained underdosing in carriers started on reduced doses and could guide safe upward titration in those who tolerate early cycles. However, the broader adoption of TDM is limited by challenges, including the instability of 5-FU in blood samples and the timing-dependent variability inherent in concentration measurements [18, 45, 46].

Phenotyping itself presents its own difficulties. In a prospective analysis of uracil-based DPD phenotyping, pre-treatment plasma uracil values differed substantially between centers and did not correlate with DPD activity in peripheral blood mononuclear cells [47]. PBMC-based assays require specialized equipment, are costly, and are not easily scalable [48, 49]. In contrast, DPYD genotyping remains a straightforward and relatively inexpensive first-line tool for identifying vulnerable individuals [7, 46, 49–51]. When accessible, phenotyping and TDM could refine dosing further—particularly in rare cases of individuals with a DPD activity score of zero, none of whom were identified in this cohort. Guidelines advise complete avoidance of fluoropyrimidines for such patients, though phenotyping and TDM may be needed to determine a safe starting dose if treatment cannot be avoided [19].

Within the prospectively genotyped population, 10 individuals (5%) were identified as variant carriers, a rate consistent with the expected prevalence based on the test panel [6]. Earlier literature has noted that the DPYD variants included in guideline recommendations were mainly validated in European cohorts. For this reason, the present study additionally incorporated variants relevant to non-European populations. This was the first prospective assessment of c.2279C>T, present in roughly 1% of people with South Asian ancestry [20], and only the second study to evaluate c.557A>G, found in approximately 3% of individuals with African ancestry [21, 22]. Although this variant was added to a US implementation program [26], prospective trial data on it remain sparse [12, 52, 53]. In the present cohort, one patient tested positive for c.557A>G, supporting its inclusion in the panel.

In this project, the development and rollout of the testing program occurred simultaneously, allowing real-time refinement of operational procedures. At the outset, DPYD status was not routinely reviewed before initiating fluoropyrimidine therapy, largely because the new testing system had not yet been fully incorporated into established clinical workflows. Many oncologists were accustomed to arranging bloodwork and scheduling chemotherapy before the first patient consultation. Although a 2-day turnaround time would effectively prevent delays, such rapid processing is not the most practical or cost-efficient method for large-scale implementation. As clinicians gained familiarity with the program, they began ordering DPYD tests prior to the initial appointment and, in selected situations, adjusted the start of chemotherapy by a few days to account for result availability.

A single oncologist may encounter many patients without ever identifying a positive DPYD result, which can weaken confidence in the value of routine genotyping [54]. Nevertheless, rare alleles do occur, and affected individuals may develop significant treatment-related harm. Within this cohort, one patient carried DPYD*13, a variant found in only 0.01% of people of European ancestry **(Table 1)**.

Close coordination between investigators and treating clinicians contributed to the strong recruitment rate, enabling prospective testing of all patients at the BC Cancer Vancouver site expected to begin fluoropyrimidine therapy. The presence of a research staff member in the clinic proved essential for recognizing eligible individuals and encouraging participation. Because of the large number of patients commencing fluoropyrimidines, this on-site team member was needed to systematically screen and obtain consent. For the first nine months, the research assistant played a key role in promoting consistent test ordering and standardized outcome documentation. When a new assay is introduced, dedicated personnel help smooth its integration into daily practice until it becomes part of clinicians' routine workflow. However, such intensive support is unlikely to be required indefinitely. After the initial period, test-ordering prompts were embedded into the electronic medical system, and testing frequency remained unchanged.

One advantage of this project is its real-world design, offering practical insights into implementing pharmacogenetic testing. A limitation, however, is that clinicians were aware of patient genotypes at the time toxicity events were recorded, which may have influenced toxicity grading. Moreover, the testing strategy captured only six DPYD variants, leaving some cases of reduced DPD function undetected. With the establishment of an in-house genotyping platform, there is future potential to expand the panel to include additional variants influencing fluoropyrimidine safety. Of potential interest is the TYMS variant rs45445694, which affects thymidylate synthase, the molecular target of 5-FU, and has been linked to higher rates of capecitabine-associated hand–foot syndrome (OR 1.32, $p < 0.0001$) [55]. Additional variants may account for the significant toxicity observed in one carrier despite guideline-recommended dose reductions, although current evidence indicates modest effect sizes and expert recommendations do not yet support routine testing. Over time, stronger data may justify their inclusion. Furthermore, variants relevant to other drugs commonly used during cancer treatment—such as TPMT and NUDT15 for thiopurines, or CYP2D6 for metoclopramide—may also eventually be incorporated [56, 57].

Another limitation was the absence of a control arm, which reduced the ability to directly quantify the clinical benefit of pre-treatment DPYD testing. However, assigning patients to an untested control group was deemed unethical, as a prior prospective study that withheld dose adjustment was halted after a DPYD carrier in the control arm died from toxicity [52]. Although the number of dose-reduced carriers in this project was insufficient for substantial statistical comparisons with patients treated at full dose, larger prospective trials have consistently demonstrated that DPYD-guided dose adjustments result in toxicity rates similar to those of non-carriers receiving standard dosing [17, 53]. These collective findings have contributed to province-wide acceptance of DPYD testing.

Overall, this study illustrates how DPYD genotyping can be operationalized, incorporated into routine clinical systems, and ultimately adopted as standard care. In summary, in conjunction with existing evidence, the results support DPYD-guided dosing as a practical and effective method to lower the likelihood of serious fluoropyrimidine toxicity in carriers of DPYD variants.

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