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Clinical Significance of DPYD Gene Polymorphism Testing in Colorectal Cancer Patients Receiving Fluoropyrimidine-Based Chemotherapy: A Single-Center Study in Latvia

Sofija Vilisova, MD
Aija Gerina, PhD
Pauls Stradiņš Clinical University Hospital, Latvia

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Abstract

Background: Fluoropyrimidine-based chemotherapy, including 5-fluorouracil (5-FU) and capecitabine, is a cornerstone of colorectal cancer (CRC) treatment. However, treatment-related toxicity varies substantially among patients and is influenced by pharmacogenetic factors. Variants in the *DPYD* gene, which encodes the enzyme dihydropyrimidine dehydrogenase (DPD), are associated with reduced enzyme activity and an increased risk of severe toxicity.

Aim: To evaluate the prevalence of clinically relevant *DPYD* polymorphisms in Latvian CRC patients receiving fluoropyrimidine-based chemotherapy and assess the clinical impact of genotype-guided dose adjustment.

Methods: This single-center observational study included 46 patients with histologically confirmed CRC treated at Pauls Stradiņš Clinical University Hospital. Patients were divided into retrospective and prospective cohorts. Genotyping was performed for four clinically relevant *DPYD* variants (c.1905+1G>A, c.1679T>G, c.2846A>T, and c.1236G>A). Clinical data, treatment modifications, and toxicity outcomes were analyzed. Toxicity was graded according to CTCAE criteria. Descriptive statistics and Pearson's chi-square test were used for statistical analysis.

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Results: Chemotherapy-related toxicity occurred in 20/46 patients (43.5%), while severe toxicity (grade 3–4) occurred in 6/46 patients (13.0%). Clinically relevant DPYD variants were detected in 2/46 patients (4.3%). One prospectively identified carrier underwent genotype-guided dose reduction, and no chemotherapy-related toxicity was observed. Age >70 years was significantly associated with dose reduction (p=0.02). The distribution of chemotherapy-related toxicity grades differed significantly across the three age groups (p = 0.042).

Conclusion: DPYD testing appears feasible and potentially useful in routine oncology practice. However, its clinical impact could not be definitively assessed in this small cohort because of the limited number of DPYD variant carriers. Larger multicenter studies are needed to determine its impact on treatment safety and toxicity reduction.

Keywords: Colorectal cancer, DPYD, pharmacogenomics, fluoropyrimidines, toxicity

Introduction

Colorectal cancer (CRC) remains one of the most commonly diagnosed malignancies worldwide and represents a major cause of cancer-related morbidity and mortality. According to global epidemiological data, CRC accounts for more than 1.9 million new cases annually and approximately 935,000 deaths worldwide, making it the third most commonly diagnosed cancer and the second leading cause of cancer-related death (Arnold et al., 2017; Sung et al., 2021). Despite improvements in screening, early detection, and treatment strategies, CRC continues to pose a significant burden on healthcare systems, particularly in regions with aging populations and changing lifestyle risk factors.

In Europe, CRC incidence and mortality rates remain high, and the disease represents a major public health concern. In Latvia, CRC is among the most frequently diagnosed malignancies, contributing substantially to cancer-related morbidity and mortality. Although national screening programs have been implemented, a considerable proportion of patients are still diagnosed at advanced stages, requiring systemic therapy.

The management of CRC involves a multidisciplinary approach, including surgery, systemic chemotherapy, targeted therapy, and radiotherapy. Among systemic treatment options, fluoropyrimidine-based chemotherapy remains a cornerstone in both adjuvant and metastatic settings (Longley et al., 2003; Van Cutsem et al., 2016). Agents such as 5-fluorouracil (5-FU) and its oral prodrug capecitabine are widely used due to their established efficacy and central role in standard treatment protocols.

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The antitumor activity of fluoropyrimidines is primarily mediated through inhibition of thymidylate synthase, resulting in impaired DNA synthesis and cell cycle arrest. Additionally, these agents are incorporated into RNA and DNA, disrupting transcriptional and translational processes and ultimately leading to tumor cell death (Longley et al., 2003). Despite their therapeutic effectiveness, fluoropyrimidines are characterized by a narrow therapeutic index and considerable interindividual variability in both efficacy and toxicity.

Fluoropyrimidine-associated toxicity represents a major clinical challenge. Approximately 10–30% of patients experience severe toxicity during treatment, including gastrointestinal toxicity, mucositis, hematological complications, neurotoxicity, and cardiotoxicity, which may lead to treatment interruption, hospitalization, and, in rare cases, treatment-related mortality (Amstutz et al., 2011; Clasen et al., 2017; Khan et al., 2023).

One of the most important determinants of fluoropyrimidine toxicity is the activity of the enzyme dihydropyrimidine dehydrogenase (DPD), which is responsible for the metabolism of approximately 80–85% of administered 5-FU (Lu et al., 1992). Reduced or absent DPD activity results in increased systemic exposure to active metabolites and a substantially elevated risk of severe toxicity (Etienne et al., 1994).

DPD activity is largely determined by genetic variation in the *DPYD* gene. Several clinically relevant variants have been identified, including c.1905+1G>A (*DPYD 2A*), c.1679T>G (*DPYD 13*), c.2846A>T, and c.1236G>A (HapB3), all of which are associated with reduced DPD activity and increased susceptibility to fluoropyrimidine-related toxicity (Henricks et al., 2018; Meulendijks et al., 2015; Offer et al., 2013). The prevalence of clinically relevant *DPYD* variants in European populations is estimated to range from 3% to 8% (Deenen et al., 2016; Henricks et al., 2018; Van Kuilenburg et al., 2002).

Over the past decade, pharmacogenomics has become an important component of precision oncology, enabling individualized treatment strategies based on genetic variability. In the context of fluoropyrimidine therapy, identification of *DPYD* variants before treatment initiation allows clinicians to adjust dosing, reduce toxicity risk, and improve treatment safety.

International guidelines, including those developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and the European Medicines Agency (EMA), recommend pre-treatment *DPYD* testing in patients receiving fluoropyrimidine-based chemotherapy (Amstutz et al., 2018; European Medicines Agency, 2020; Lunenburg et al., 2020). Increasing evidence demonstrates that genotype-guided dosing significantly reduces the incidence

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of severe toxicity while maintaining treatment efficacy (Deenen et al., 2016; Henricks et al., 2018).

Despite these advances, implementation of pharmacogenetic testing remains inconsistent across healthcare systems because of cost considerations, limited access to testing, and the absence of standardized national protocols. In Latvia, routine *DPYD* testing has not yet been fully integrated into clinical practice, and real-world data regarding its clinical utility remain limited.

Therefore, the aim of this study was to evaluate the prevalence of clinically relevant *DPYD* gene polymorphisms in Latvian colorectal cancer patients receiving fluoropyrimidine-based chemotherapy and to assess the clinical significance and real-world impact of genotype-guided dose adjustment strategies in routine oncology practice.

Methods

Study Design and Setting

This study was conducted as a single-center observational cohort study at Pauls Stradiņš Clinical University Hospital, a tertiary care institution providing specialized oncological services in Latvia. The study design incorporated both retrospective and prospective components, allowing evaluation of clinical outcomes before and after the implementation of pharmacogenetic testing in routine clinical practice.

The retrospective cohort comprised patients selected chronologically from multidisciplinary tumor board records from 2021 to 2022. The prospective cohort included patients recruited from 4 September 2023 to 31 December 2024 who underwent DPYD genotyping before the initiation of fluoropyrimidine-based chemotherapy. Patients in both cohorts were followed throughout the course of fluoropyrimidine-based chemotherapy, from treatment initiation until treatment completion or discontinuation. This approach enabled assessment of the real-world clinical impact of genotype-guided treatment strategies.

Study Population

A total of 46 adult patients with histologically confirmed colorectal cancer were included in the study. Colorectal cancer was diagnosed based on histopathological examination of tumor tissue obtained by endoscopic biopsy or surgical resection, in accordance with international clinical guidelines (Argilés et al., 2020). Patients were treated at Pauls Stradiņš Clinical University Hospital and had either received or were scheduled to receive fluoropyrimidine-based chemotherapy. No formal sample size calculation was performed because of the exploratory nature of the study. The sample size was determined by the number of eligible patients available at the study center

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during the predefined study periods and the limited availability of DPYD testing during its initial implementation in routine clinical practice.

Inclusion criteria were:

- age ≥18 years
- histologically confirmed colorectal cancer
- treatment with fluoropyrimidine-based chemotherapy (5-fluorouracil or capecitabine)
- availability of clinical and treatment-related data

Exclusion criteria included:

- incomplete or missing clinical data
- prior discontinuation of treatment due to non-treatment-related factors

All patients included in the prospective cohort provided written informed consent prior to participation in the study.

DPYD Genotyping

Peripheral venous blood samples were collected in EDTA-containing tubes prior to the initiation of chemotherapy. Genomic DNA was extracted using the QIAcube HT system and the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA concentration was measured using the NanoPhotometer N60 (Implen, Munich, Germany). DPYD genotyping was performed using a real-time polymerase chain reaction (RT-PCR)-based commercial assay (gb PHARM DPYD kit, catalogue No. 3255-025) according to the manufacturer's instructions. Amplification and genotype detection were performed using the CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). The assay targeted four clinically relevant DPYD variants: c.1905+1G>A (DPYD*2A), c.1679T>G (DPYD*13), c.2846A>T, and c.1236G>A (HapB3). These variants were selected based on their established clinical relevance and association with reduced DPD enzyme activity and an increased risk of fluoropyrimidine-related toxicity, as reported in international pharmacogenetic guidelines. The commercial assay included wild-type, heterozygous, and mutant controls, which were used in accordance with the manufacturer's instructions for analytical quality control. All analyses were performed according to standardized laboratory protocols.

Clinical Data Collection

Clinical data were obtained retrospectively from patient medical records and prospectively from clinical documentation.
The following variables were collected and analyzed:

- demographic characteristics (age, sex)
- tumor characteristics (location, stage)

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- treatment regimens (type of fluoropyrimidine, combination therapy)
- chemotherapy dose and dose modifications
- occurrence and severity of treatment-related toxicity

For descriptive analyses, patients were stratified into two age groups (≤70 and >70 years). For analysis of chemotherapy-related toxicity grades, patients were categorized into three age groups (40–49, 50–69, and ≥70 years).

Assessment of Toxicity

Chemotherapy-related toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE). Toxicity was categorized into:

- any-grade toxicity
- severe toxicity (grade 3–4)

Specific types of toxicity included gastrointestinal toxicity, hematological toxicity, neurotoxicity, and thrombotic complications.
All toxicity events were recorded and analyzed in relation to patient characteristics and treatment parameters.

Treatment and Dose Modification

Fluoropyrimidine-based chemotherapy was administered according to standard clinical protocols. In the retrospective cohort, treatment decisions were based on standard clinical assessment without pharmacogenetic guidance. In the prospective cohort, DPYD genotype-guided dose adjustment was performed according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations (Amstutz et al., 2018).

Patients with a normal DPYD activity score of 2.0 received the standard fluoropyrimidine dose. For heterozygous carriers of reduced-function variants, including c.2846A>T and c.1236G>A (HapB3), corresponding to a DPYD activity score of 1.5, an initial fluoropyrimidine dose reduction of 50% was recommended, followed by dose titration based on treatment tolerance and toxicity. For heterozygous carriers of no-function variants, including c.1905+1G>A (DPYD2A) and c.1679T>G (DPYD13), corresponding to a DPYD activity score of 1.0, an initial dose reduction of 50% was recommended, followed by dose titration according to clinical tolerance. Fluoropyrimidines were avoided in patients with complete DPD deficiency.

In the present prospective cohort, one patient was identified as a heterozygous carrier of the c.1236G>A (HapB3) variant, and the initial fluoropyrimidine dose was reduced in accordance with these recommendations. Dose reduction was defined as any decrease from the initially planned chemotherapy dose.

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Statistical Analysis

Statistical analyses were performed using Microsoft Excel 365 with the Data Analysis ToolPak (Microsoft Corporation, Redmond, WA, USA). Descriptive statistics were used to summarize demographic characteristics, clinical variables, treatment parameters, DPYD genotype distribution, and toxicity outcomes. Categorical variables were presented as frequencies and percentages, whereas continuous variables were summarized using means and ranges.

Associations between categorical variables were assessed using Pearson's chi-square (χ^2) test. The distribution of chemotherapy-related toxicity grades (grade 0–4) was compared across three age groups (40–49, 50–69, and ≥70 years) using Pearson's chi-square test. Associations between age group and dose reduction were also evaluated. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Due to the limited sample size and the small number of DPYD variant carriers, multivariable analyses were not performed. The results should therefore be interpreted as exploratory and hypothesis-generating.

Because only two patients carried clinically relevant DPYD variants, no formal statistical comparison between DPYD variant carriers and non-carriers was performed. Descriptive reporting was considered more appropriate than inferential statistical testing in this subgroup because of the very small expected cell counts.

Ethical Considerations

The study was reviewed and approved by the Central Medical Ethics Committee of Latvia and registered with the Ministry of Health under registration No. 7611. A favorable ethical opinion was issued on 4 September 2023 (Protocol No. 2023-5). The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients included in the prospective cohort provided written informed consent prior to participation. Patient confidentiality was maintained throughout the study, and all data were anonymized prior to analysis.

Results

Patient Characteristics

A total of 46 patients with histologically confirmed colorectal cancer were included in the study. The baseline characteristics of the study population are summarized below.

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Table 1: Baseline Characteristics of the Study Population According to DPYD Genotype Status

Characteristic	No DPYD Variant Detected (n = 44)	DPYD Variant Detected (n = 2)
Sex, n (%)		
Female	**28 (63.6)**	**1 (50.0)**
Male	**16 (36.4)**	**1 (50.0)**
Age, years		
Mean (range)	**65.6 (42–84)**	**62.0 (51–73)**
Age group, n (%)		
40-49 years	**2 (4.5)**	**0 (0.0)**
50-69 years	**23 (52.3)**	**1 (50.0)**
≥70 years	**19 (43.2)**	**1 (50.0)**
Diagnosis, n (%)		
C18 (Colon cancer)	**28 (63.6)**	**2 (100.0)**
C19 (Rectosigmoid junction cancer)	**5 (11.4)**	**0 (0.0)**
C20 (Rectal cancer)	**11 (25.0)**	**0 (0.0)**

Abbreviations: DPYD, dihydropyrimidine dehydrogenase gene

Statistical comparisons between patients with and without clinically relevant DPYD variants were not performed because only two patients carried a DPYD variant, precluding meaningful statistical analysis. Baseline characteristics of the study population are summarized in Table 1. Overall, 29/46 patients (63.0%) were female, and the mean age was 65.4 years.

DPYD Genotype Distribution

Analysis of DPYD gene polymorphisms revealed that 2/46 patients (4.3%) carried a clinically relevant DPYD variant. No other clinically significant DPYD variants (c.1905+1G>A, c.1679T>G, or c.2846A>T) were detected in this cohort.

Cohort Distribution and DPYD Testing Strategy

Of the 46 patients included in the study, 17/46 (37.0%) underwent retrospective DPYD testing after initiation or completion of fluoropyrimidine-based chemotherapy, whereas 29/46 patients (63.0%) underwent prospective DPYD testing before treatment initiation. In the retrospective cohort, 1/17 patient (5.9%) was identified as carrying the c.1236G>A (HapB3) variant. This patient received the full standard fluoropyrimidine dose and did not develop chemotherapy-related toxicity.

In the prospective cohort, 1/29 patient (3.4%) was identified as a heterozygous carrier of the c.1236G>A (HapB3) variant. Chemotherapy dosing was adjusted according to institutional pharmacogenetic recommendations. No chemotherapy-related toxicity was observed in this patient.

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Table 2: Comparison of Retrospective and Prospective Cohorts

Variable	Retrospective (n=17)	Prospective (n=29)
Patients, n	**17**	**29**
DPYD variant carriers, n (%)	**1 (5.9)**	**1 (3.4)**
Variant detected	**c.1236G>A (HapB3)**	**c.1236G>A (HapB3)**
Genotype-guided dose reduction, n	**0**	**1**
Toxicity among DPYD carriers, n	**0**	**0**
Severe toxicity among DPYD carriers, n	**0**	**0**

Chemotherapy-Related Toxicity

Chemotherapy-related toxicity was observed in 20/46 patients (43.5%). Severe toxicity (grade 3–4) occurred in 6/46 patients (13.0%). The most commonly observed toxicities included gastrointestinal toxicity, such as diarrhea and mucositis, as well as peripheral neuropathy and thrombotic complications.

Dose Modification

Dose reduction was required in 13/46 patients (28.3%).
A statistically significant association was observed between age >70 years and dose reduction ($p = 0.02$).

Association Between Age and Toxicity

The distribution of chemotherapy-related toxicity grades differed significantly among the three age groups (40–49, 50–69, and ≥70 years, $p = 0.042$). Severe toxicity (grade 3–4) occurred in 1/2 patients aged 40–49 years (50.0%), 4/24 patients aged 50–69 years (16.7%), and 1/20 patients aged ≥70 years (5.0%).

Impact of Genotype-Guided Dose Adjustment

In the prospective cohort, genotype-guided dose adjustment was implemented in the patient carrying the c.1236G>A (HapB3) variant. No chemotherapy-related toxicity was observed in this patient.

Discussion

This study provides real-world data regarding the feasibility of implementing DPYD pharmacogenetic testing in colorectal cancer patients receiving fluoropyrimidine-based chemotherapy. Although conducted in a single-center setting with a relatively limited sample size, the findings are consistent with previously published data and demonstrate the practical implementation of DPYD testing in routine oncology practice.

The observed prevalence of clinically relevant DPYD variants in this study (2/46; 4.3%) is consistent with previously reported data from European populations, where the prevalence ranges from approximately 3% to 8%

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(Deenen et al., 2016; Henricks et al., 2018; Van Kuilenburg et al., 2002). This finding suggests that the Latvian population does not substantially differ from other European populations regarding the distribution of clinically relevant DPYD variants. However, the relatively low number of detected variants may also reflect the limited sample size and the restricted number of variants included in the genotyping panel. Previous studies have demonstrated that rare and less frequently tested DPYD variants may also contribute to fluoropyrimidine-related toxicity (Cui et al., 2025).

Two patients carrying clinically relevant DPYD variants were identified in this study. One patient was identified retrospectively and received the standard fluoropyrimidine dose, whereas one patient was identified prospectively and underwent genotype-guided dose adjustment. Neither patient experienced chemotherapy-related toxicity. However, given the small sample size and the low number of variant carriers, no definitive conclusions regarding the clinical benefit of genotype-guided dose adjustment can be drawn. Although these findings are consistent with previously published prospective studies demonstrating that genotype-guided dosing strategies can reduce the risk of severe fluoropyrimidine-associated toxicity while maintaining treatment efficacy (Boisdron-Celle et al., 2017; Deenen et al., 2016; Henricks et al., 2018), the present study was not designed or powered to confirm these benefits. Larger multicenter studies are therefore required to further evaluate the clinical impact of genotype-guided dosing.

The predominance of the c.1236G>A (HapB3) variant observed in this study is also in agreement with findings from other European cohorts, where HapB3 represents one of the most frequently detected DPYD variants (Lunenburg et al., 2020; Meulendijks et al., 2015). However, recent pharmacogenomic research has highlighted the complexity of predicting fluoropyrimidine toxicity. Emerging evidence suggests that additional rare variants may contribute to reduced DPD activity and toxicity risk, supporting the need for continuous refinement of pharmacogenetic testing panels (Cui et al., 2025).

An interesting finding of this study was that the distribution of chemotherapy-related toxicity grades differed significantly among the three age groups. Numerically, patients aged ≥70 years experienced fewer grade 3–4 toxicities than younger patients. However, this observation should be interpreted cautiously because of the small sample size and the markedly unequal distribution of patients across age groups, particularly the very small number of patients aged 40–49 years. Therefore, no definitive conclusions regarding the relationship between age and severe toxicity can be drawn from this study.

From a clinical perspective, the results emphasize the importance of integrating pharmacogenetic testing into routine oncology practice.

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Fluoropyrimidine-associated toxicity may result in treatment interruption, dose reduction, hospitalization, and, in severe cases, treatment-related mortality. Identification of patients at increased risk before treatment initiation represents an important component of safer and more personalized cancer therapy.

Beyond individual patient benefits, implementation of DPYD testing may also have important implications for healthcare systems. Prevention of severe toxicity can reduce hospital admissions, supportive care requirements, and treatment delays, thereby decreasing healthcare expenditures. Several studies have demonstrated the cost-effectiveness of genotype-guided fluoropyrimidine dosing strategies (Brooks et al., 2022; Deenen et al., 2016). Therefore, pharmacogenetic testing may provide both clinical and economic benefits.

Several limitations of this study should be acknowledged. First, the relatively small sample size limits statistical power and may affect the generalizability of the findings. Second, only four clinically relevant DPYD variants were analyzed, potentially underestimating the true prevalence of actionable genetic variation. Third, the observational design does not allow definitive conclusions regarding causality. Furthermore, the single-center design and the combination of retrospective and prospective cohorts may have introduced heterogeneity in patient management and data collection, limiting the generalizability of the findings.

Future studies should include larger multicenter cohorts and expanded genotyping panels to provide a more comprehensive assessment of DPYD variability. Integration of pharmacogenetic data with additional clinical and molecular markers may further improve risk stratification and treatment individualization.

Overall, the findings of this exploratory single-center study suggest that pre-treatment DPYD pharmacogenetic testing is feasible and may represent a useful component of personalized treatment planning for patients receiving fluoropyrimidine-based chemotherapy. However, because only two patients carried clinically relevant DPYD variants and only one underwent prospective genotype-guided dose adjustment, this study was not powered to assess the clinical effectiveness of genotype-guided dosing, and no definitive conclusions regarding its clinical benefit can be drawn. Larger multicenter prospective studies are required to confirm these findings.

Conclusions

Clinically relevant DPYD variants were detected in 2/46 patients (4.3%). The implementation of pre-treatment DPYD testing was feasible in routine oncology practice and allowed genotype-guided dose adjustment in one prospectively identified variant carrier. Although no severe toxicity was

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observed among DPYD variant carriers in this cohort, the limited sample size prevents definitive assessment of the impact of genotype-guided dosing on treatment safety. These findings suggest the potential clinical utility of DPYD testing and should be further evaluated in larger multicenter studies.

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Declaration for Human Participants: The study was reviewed and approved by the Central Medical Ethics Committee of Latvia. The study was registered with the Ministry of Health under registration No. 7611 and received a favorable ethical opinion on 4 September 2023 (Protocol No. 2023-5). The study was conducted in accordance with the Declaration of Helsinki.

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