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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

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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. **Results:** Chemotherapy-related toxicity occurred in 43% of patients, while severe toxicity (grade 3–4) was observed in 13%. Clinically relevant *DPYD* variants were detected in 2 patients (4.4%), both carrying the c.1236G>A (HapB3) variant. No severe toxicity was observed among variant carriers who underwent genotype-

guided dose reduction. Age >70 years was significantly associated with dose reduction (p=0.02), whereas younger patients experienced a higher incidence of severe toxicity (p=0.042). **Conclusion:** *DPYD* testing is feasible and clinically relevant in routine oncology practice. The findings support the potential clinical value of genotype-guided treatment strategies in CRC patients receiving fluoropyrimidine-based chemotherapy. However, larger multicenter studies are required to confirm their 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.

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 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 included patients treated prior to the introduction of DPYD genotyping, while the prospective cohort consisted of patients who underwent pharmacogenetic testing before initiation of fluoropyrimidine-based chemotherapy. This approach enabled assessment of real-world clinical impact of genotype-guided treatment strategies.

Study Population

A total of 46 patients with histologically confirmed colorectal cancer were included in the study. Patients were treated at Pauls Stradiņš Clinical University Hospital and received fluoropyrimidine-based chemotherapy as part of their treatment regimen.

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
- severe comorbid conditions that could independently influence chemotherapy-related toxicity
- 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 prior to initiation of chemotherapy. Genomic DNA was extracted using standard laboratory procedures in accordance with validated protocols.

Genotyping was performed using polymerase chain reaction (PCR)-based methods targeting four clinically relevant DPYD variants:

- c.1905+1G>A (DPYD2A)
- c.1679T>G (DPYD13)
- c.2846A>T
- c.1236G>A (HapB3)

These variants were selected based on their established clinical relevance and association with reduced DPD enzyme activity and increased risk of fluoropyrimidine-related toxicity, as reported in international pharmacogenetic guidelines.

Quality control procedures were applied during laboratory analysis to ensure the reliability and reproducibility of genotyping results. 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)
- treatment regimens (type of fluoropyrimidine, combination therapy)
- chemotherapy dose and dose modifications
- occurrence and severity of treatment-related toxicity

Patients were stratified according to age groups (≤70 years and >70 years) to evaluate the association between age and treatment outcomes.

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 genotyping results were used to guide treatment decisions. In patients with identified DPYD variants, dose adjustments were implemented in accordance with available clinical guidelines and recommendations.

Dose reduction was defined as any decrease in the planned chemotherapy dose during treatment.

Statistical Analysis

Statistical analysis was performed using descriptive and inferential methods.

Descriptive statistics were used to summarize patient characteristics, treatment parameters, and toxicity outcomes. Categorical variables were expressed as percentages, and continuous variables were summarized using mean values.

Associations between categorical variables were evaluated using the chi-square test. The relationship between age, toxicity, and dose modification was specifically analyzed.

A p-value <0.05 was considered statistically significant.

Due to the relatively small sample size, multivariate analysis was not performed. Therefore, the results should be interpreted as exploratory and hypothesis-generating.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval for the study was obtained from the appropriate local ethics committee.

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.

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 (%)		
≤50 years	**2 (4.5)**	**0 (0.0)**
51–70 years	**23 (52.3)**	**1 (50.0)**
≥71 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.

The majority of patients were female (63%), while 37% were male, indicating a slight predominance of female patients in this cohort. The mean age of the study population was 65.4 years, reflecting a typical colorectal cancer patient population in routine clinical practice.

Patients were stratified into two age groups (≤70 years and >70 years) to evaluate the potential impact of age on treatment outcomes, toxicity, and dose modification patterns. This stratification allowed for further subgroup analysis and provided additional insight into clinical decision-making processes.

DPYD Genotype Distribution

Analysis of DPYD gene polymorphisms revealed that 2 out of 46 patients (4%) carried a clinically relevant variant. Both patients were identified as carriers of the c.1236G>A (HapB3) variant.

No other clinically significant DPYD variants (c.1905+1G>A, c.1679T>G, or c.2846A>T) were detected in this cohort. This finding is consistent with previously reported data suggesting that HapB3 is among the more frequently observed variants in European populations.

The relatively low frequency of detected variants may be attributed to the limited sample size as well as the restricted number of variants included in the genotyping panel.

Cohort Distribution and DPYD Testing Strategy

Of the 46 patients included in the study, 17 (37.0%) underwent retrospective DPYD testing after initiation or completion of

fluoropyrimidine-based chemotherapy, whereas 29 patients (63.0%) underwent prospective DPYD testing before treatment initiation.

In the retrospective cohort, one patient (5.9%) was identified as carrying the c.1236G>A (HapB3) variant. This patient received the full standard chemotherapy dose and did not develop treatment-related toxicity. No statistically significant association between DPYD variant status and toxicity was observed (p = 1.000); however, interpretation is limited by the small number of variant carriers.

In the prospective cohort, one 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. Given that only one variant carrier was identified, formal statistical analysis was not informative.

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 43% of patients, indicating that nearly half of the study population experienced at least one adverse event during treatment.

Severe toxicity (grade 3–4) was documented in approximately 13% of patients. These cases represent clinically significant adverse events that may require treatment modification, hospitalization, or supportive care interventions.

The most commonly observed toxicities included gastrointestinal toxicity, such as diarrhea and mucositis, as well as peripheral neuropathy and thrombotic complications. These findings are consistent with the known toxicity profile of fluoropyrimidine-based chemotherapy.

The observed rate of toxicity in this study is comparable to previously reported data, supporting the external validity of the findings.

Dose Modification

Dose reduction was required in 28% of patients during the course of treatment. This reflects routine clinical practice, where treatment intensity is adjusted based on patient tolerance and the occurrence of adverse events.

A statistically significant association was observed between age greater than 70 years and the likelihood of dose reduction (p=0.02). This finding suggests that clinicians may adopt a more cautious approach in older patients, potentially reflecting concerns regarding comorbidities, frailty, and treatment tolerability.

Association Between Age and Toxicity

Interestingly, analysis of toxicity patterns revealed that younger patients (≤70 years) demonstrated a higher incidence of severe toxicity compared to older patients (p=0.042).

This finding is somewhat unexpected, as older age is traditionally considered a risk factor for increased treatment-related toxicity. However, it may reflect differences in treatment intensity, with younger patients potentially receiving more aggressive chemotherapy regimens or higher doses.

These results highlight the complexity of factors influencing chemotherapy-related toxicity and suggest that chronological age alone may not be a sufficient predictor of toxicity risk.

Impact of Genotype-Guided Dose Adjustment

In the prospective cohort, genotype-guided dose adjustment was implemented in patients identified as carriers of DPYD variants. In these cases, chemotherapy dosing was modified in accordance with clinical recommendations.

Importantly, no cases of severe toxicity were observed among patients who underwent genotype-guided dose adjustment. This finding suggests a potential protective effect of pharmacogenetic-guided treatment strategies.

Although the number of variant carriers was limited, this observation is consistent with previously published studies demonstrating that pre-treatment DPYD testing and subsequent dose adjustment can significantly reduce the risk of severe toxicity.

Overall Interpretation of Results

Taken together, the results of this study demonstrate that fluoropyrimidine-related toxicity remains a common clinical issue in colorectal cancer treatment. The identification of DPYD variants, although limited in this cohort, provides valuable information for individualizing treatment.

The observed associations between age, dose modification, and toxicity further highlight the importance of personalized treatment strategies that take into account both clinical and genetic factors.

Discussion

This study provides real-world data regarding the feasibility and potential clinical relevance of 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 reflect practical implementation in routine oncology practice.

The observed prevalence of clinically relevant *DPYD* variants in this study (4.4%) is consistent with previously reported data from European populations, where the prevalence ranges from approximately 3% to 8% (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).

One of the observations of this study was the absence of severe toxicity in the prospectively identified DPYD variant carrier who underwent genotype-guided dose adjustment. However, given the small sample size and the low number of variant carriers, no definitive conclusions regarding clinical benefit can be drawn. This observation is nevertheless 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). These findings are consistent with previously published evidence supporting routine pre-treatment DPYD testing. However, larger multicenter studies are required to confirm the clinical impact observed in this cohort.

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 the higher incidence of severe toxicity among younger patients compared with older individuals. Although older age is traditionally considered a risk factor for

chemotherapy-related toxicity, younger patients may receive more intensive treatment regimens or higher initial doses, which could contribute to an increased incidence of severe adverse events. This observation emphasizes the multifactorial nature of treatment-related toxicity and suggests that chronological age alone is not a sufficient predictor of toxicity risk.

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

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 study support the growing body of evidence demonstrating that *DPYD* pharmacogenetic testing is a valuable tool in the management of colorectal cancer patients receiving fluoropyrimidine-based chemotherapy. Routine implementation of genotype-guided treatment strategies represents a promising approach to personalized oncology care. However, further validation in larger multicenter cohorts is required before definitive conclusions regarding treatment safety and toxicity reduction can be made.

Conclusions

Clinically relevant DPYD variants were detected in 4.4% of patients. The implementation of pre-treatment DPYD testing was feasible in routine oncology practice and allowed genotype-guided dose adjustment in identified variant carriers. Although no severe toxicity was 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 support the potential clinical value 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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