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LETTER TO THE EDITOR

Dihydropyrimidine dehydrogenase (DPD) genotype and phenotype among Danish cancer patients: prevalence and correlation between *DPYD*-genotype variants and P-uracil concentrations

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Background

Fluoropyrimidines are the cornerstone of the chemotherapeutic treatment of several gastrointestinal, solid tumors [1,2]. The essential fluoropyrimidines include 5-fluorouracil (5-FU) and the oral prodrugs capecitabine and tegafur (the active substance of Teysuno(S-1), all metabolized by the rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD). This group of fluoropyrimidines will be referred to as FP.

Observational studies have shown that cancer patients with decreased DPD-activity are at elevated risk of experiencing severe adverse events if treated with standard doses of FP [3]. Systemic FP-associated toxicities include neutropenia, diarrhea, cardiotoxicity, and Palmar-Plantar Erythrodysesthesia [4,5].

France was in 2018 the first country to make pretreatment DPD testing mandatory [6]. In spring 2020, The European Medicines Agency (EMA) and later The Danish Medicines Agency (DMA) recommended testing all patients for DPD-deficiency before initiating treatment with FP [7,8].

DPD-testing was implemented as standard clinical care in Denmark the following months using genotype-testing of *DPYD,* the gene encoding DPD, and/or a measurement of the endogenous metabolite uracil (DPD-phenotype test). Both methods have strengths and limitations [9]. The recommended starting dose of FP for patients diagnosed with partial DPD-deficiency is 50% [10,11]. Treatment with FP is contraindicated in patients with complete DPD-deficiency due to a high risk of life-threatening adverse events [10,11].

The standard *DPYD*-genotype analysis include testing of four different variants known to be associated with DPD activity following the EMA and DMA. The analysis of these four variants shown in Table 1 can be performed relatively easy using commercially available kits. However, other rare variants which could potentially also affect the DPD activity are not investigated as a standard in most laboratories as this requires more time-consuming methods. Patients that are heterozygous for one variant correspond to partial DPD deficiency. Patients who are homozygous for one variant or compound heterozygous (patients with $\geq$2 different variant SNPs) are categorized as having complete DPD deficiency [10,11].

The DPD-phenotype can be measured using different methods, including dihydrouracil/uracil ratio, uracil measurements in saliva, or uracil in plasma. The latter method was

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implemented into clinical practice in Denmark because it is commonly used in Europe and is recommended by the EMA [6,7,9,12]. The physiological role of the DPD-enzyme is to metabolize the two endogenous pyrimidines, thymine, and uracil, leading to an elevated plasma-uracil concentration ([U]) in patients with DPD-deficiency. [U] is affected by food intake and circadian rhythm [13,14] and is significantly increased in patients with end-stage renal disease [15]. The [U] concentration may also be affected in patients with tumor lysis syndrome, where a pronounced increase in [U] has been reported [16]. Furthermore, [U] is not stable in whole blood, so plasma must be isolated immediately after blood sampling and stored at −20 °C or analyzed. Incorrect or prolonged handling of samples could lead to falsely elevated [U] values [17]. Recently, De With *et al.* found significant between-center variance in pretreatment [U], underlining that measurement of [U] can be susceptible to preanalytical errors as well as the difference between unstandardized methods [18]. Patients with [U] $\geq$ 16 ng/mL and >150 ng/mL are categorized as having partial DPD deficiency and complete DPD deficiency, respectively [19].

Here we report the prevalence of clinically relevant *DPYD*-genotype variants and the correlation between these genotype variants and the DPD-phenotype ([U]) based on all available Danish patient samples collected since the implementation of the analysis.

Material & methods

We collected data from all Danish hospital laboratories ($n = 6$) performing clinical DPD-testing: Rigshospitalet, University Hospital of Southern Denmark, Lillebaelt Hospital, Odense University Hospital, Aarhus University Hospital, Aalborg University Hospital, and Zealand University Hospital.

We collected laboratory results from 1st July 2020 to 31st December 2021. We included all samples from patients who had been tested for DPD-deficiency during the study period. All tests had been prescribed in a clinical setting in cancer patients who had an indication for systemic treatment with FP. For information regarding the statistics used see ***Appendix 1*** (Supplementary Material)**.**

DPYD-genotype

Patients were genotyped for the clinically relevant *DPYD*-variants shown in Table 1 Testing for these variants is recommended by The Dutch Pharmacogenetics Working Group (DPWG), Clinical Pharmacogenetics Implementation Consortium and EMA [7,10,11].

Uracil measurements (DPD-phenotype)

Four laboratories measured [U] using Liquid chromatography-mass spectrometry (LC-MS). No consideration was taken to what time of day the blood samples were drawn or if the patient was fasting. For data analysis, all values below 5 ng/mL were coded as 2.5 ng/mL.

For further details regarding the phenotyping and *DPYD*-genotyping methods used at the different hospital laboratories, see ***Appendix 1*** (Supplementary Material)**.**

Results

In the data collection period (18 months), 4228 Danish patients had their DPD-activity assessed by either the *DPYD*-genotype and/or phenotype test. Because of different testing strategies at the enrolled hospital laboratories, 1985 patients were tested with either [U] ($n = 17$) or *DPYD*-genotype ($n = 1968$), while the remaining 2243 patients were tested with both methods. For further information, see Supplementary Table 1.

Of the 4215 *DPYD*-genotyped patients, 3895 (92.4%) were wild type, and 316 (7.5%) were heterozygous for one of the *DPYD*-variants. Four patients (0.1%) were compound heterozygous and zero homozygous patients were identified.

Table 1. Distribution of tested DPYD-variants.

Overall *DPYD*-genotype distribution

	DPD-activity	Number of individuals	%
Wild type	Normal DPD-activity	3895	92.4
Heterozygous	Partial DPD-deficiency,	316	7.5
Compound heterozygous*	Partial or complete DPD-deficiency	4	0.1
Homozygous	Complete DPD deficiency	0	0
Total		4215	100

Distribution of specific *DPYD* genotypes

rs number (alternative name)	HGVS (c.)	HGVS (p.)	Number of individuals	% of total
rs3918290 (*DPYD**2A) / wild type	c.1905 + 1G > A		43	1.0
rs67376798 (D949V) / wild type	c.2846A > T	p.(Asp949Val)	57	1.4
rs55886062 (*DPYD**13) / wild type	c.1679T > G	p.(Ile560Ser)	8	0.2
rs56038477 (HapB3)** / wild type	c.1236G > A	p.(Glu412Glu)	208	4.9
rs67376798 / rs56038477 (HapB3)**	c.2846A > T / c.1236G > A	p.(Asp949Val)/p.(Glu412Glu)	3	<0.01
rs3918290 (*DPYD**2A) / rs56038477 (HapB3)**	c.1905 + 1G > A / c.1236G > A	p.(Glu412Glu)	1	<0.01

*With the employed methods it is not possible to determine if a patient is in fact compound heterozygous or whether the two variants are *in cis*. Thus, all patients with more than one *DPYD* variant identified are categorized as compound heterozygous in this study.

**The variant rs56038477 is part of the hapB3 haplotype and shown to be in strong linkage disequilibrium with rs75017182 in Europeans (Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, *et al.* Clinical pharmacogenetics implementation consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 Update. Clin Pharmacol Therapeut. (2018) 103:210–6. doi: 10.1002/cpt.911).

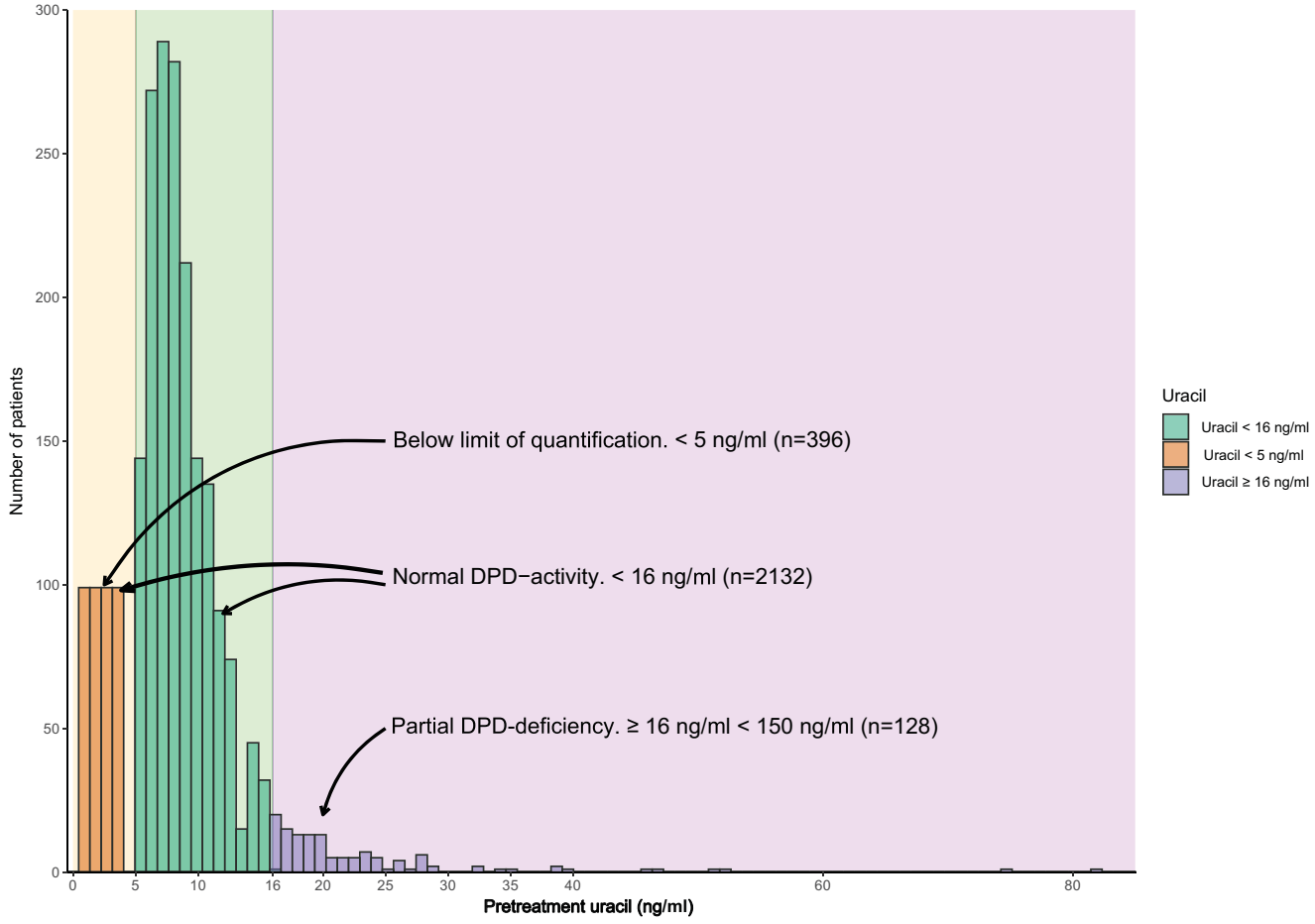

Figure 1. Distribution of P-uracil concentrations ($n = 2260$).

Table 1 shows the distribution of the *DPYD*-variants. For information regarding the prevalence of *DPYD*-variant across hospital laboratories, see Supplementary Table 2.

Of the 2260 phenotyped patients, 2132 (94.3%) had an [U] below 16 ng/mL. The remaining 128 (5.7%) patients had uracil concentrations ≥16 ng/mL and <150 ng/mL. No values above 150 ng/mL were found. Median uracil concentration was 8 ng/mL (range 2.5–82 ng/mL). Figure 1 shows the distribution of [U].

When comparing the [U] analyzed at the different laboratories **(**Supplementary Figure S1**)**, we found some variation. Aarhus University Hospital measured significantly lower median [U] values than the others.

Correlation between DPYD-genotype variants and [U]

In patients with both geno- and phenotype data, the median [U] among patients without one of the four investigated *DPYD*-variants (wild type) was significantly lower (7.5 ng/mL) compared to patients with *DPYD*-variants (9.6 ng/mL), median difference 2.5 ng/mL, 95% CI; 2.0–3.1 ng/mL, ($p = 2.95e-13$) (Figure 2(A)).

In Figure 2(B), the distribution of [U] by *DPYD*-variants is illustrated ($p = 2.35e-15$). In 4.8% ($n = 99$) of the *DPYD*-wild type patients, the [U] was ≥16 ng/mL compared to 16.8% ($n = 29$) in the group with *DPYD*-variants. For further details, see Supplementary Table 3. All three compound heterozygous patients had [U] below 16 ng/mL, indicating a normal DPD-activity is based solely on the phenotyping method.

Discussion

We here report the first Danish data on the prevalence of DPD-deficiency in a non-selected group of 4228 cancer patients. We found that 7.5% of the patients carried one of the clinically relevant *DPYD*-variants, and 5.7% had [U] between ≥16 ng/mL and <150 ng/mL.

The prevalence of DPD-deficiency in Europe has been described in two extensive studies from France and the Netherlands. The reported prevalence of the four clinically relevant *DPYD* variants was 4.7% [20] and 7.7% [21] in a non-selected group of patients. Pallet *et al.* [20] also examined the [U] ($n = 3680$ patients) and found that 6.8% of the patients had DPD deficiency (>16 ng/mL) and two patients (0.05%) had complete DPD deficiency (>150 ng/mL). The study found a poor correlation between *DPYD*-variants and [U] but included no clinical data regarding FP toxicity [20].

As for the distribution of [U], our data appear comparable with other European studies on unselected populations of cancer patients [20]. Meulendijks *et al.* found that among 550 Dutch cancer patients in The Netherlands, 3.1% had [U] above 16 ng/mL. However, the true prevalence is probably

Figure 2A. Distribution of uracil concentration between wild type and *DPYD*-variant carriers. The red dotted line represents the cut-off value of 16 ng/ml

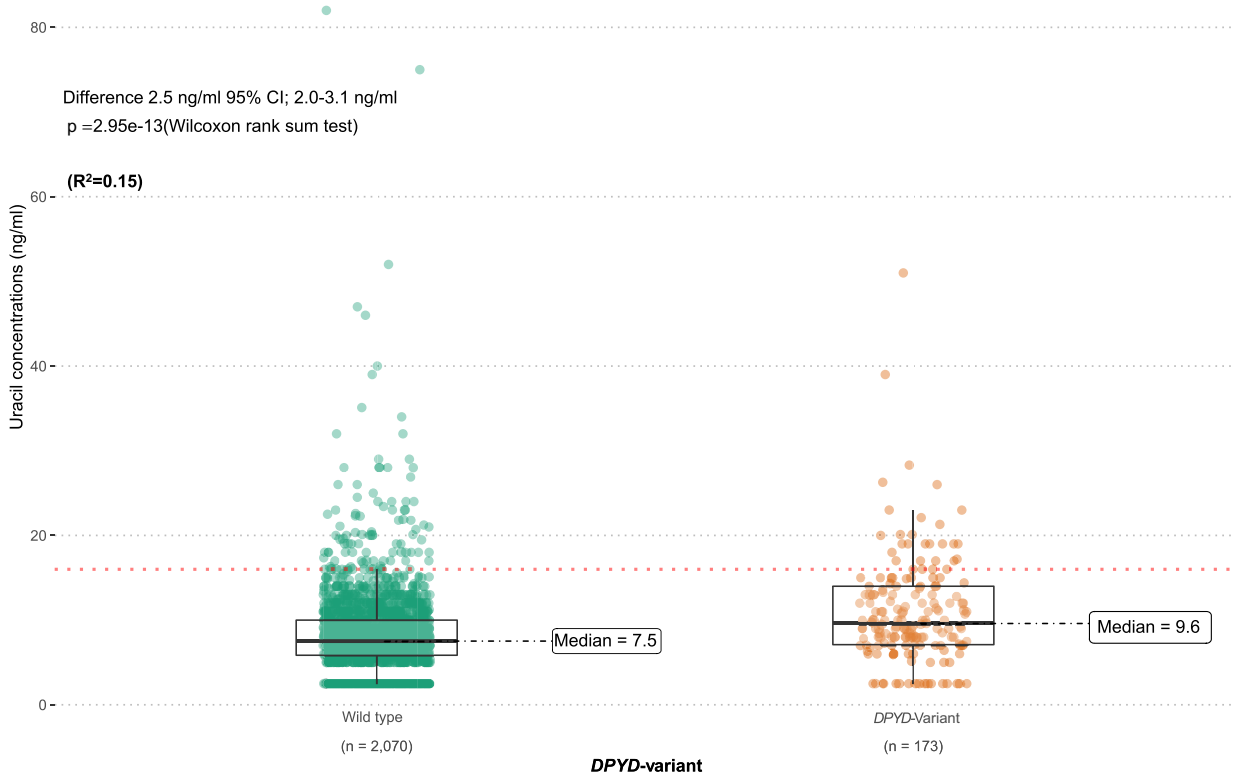

Figure 2B. Distribution of uracil concentration across specific *DPYD*-variants The red dotted line represents the cut-off value of 16 ng/ml

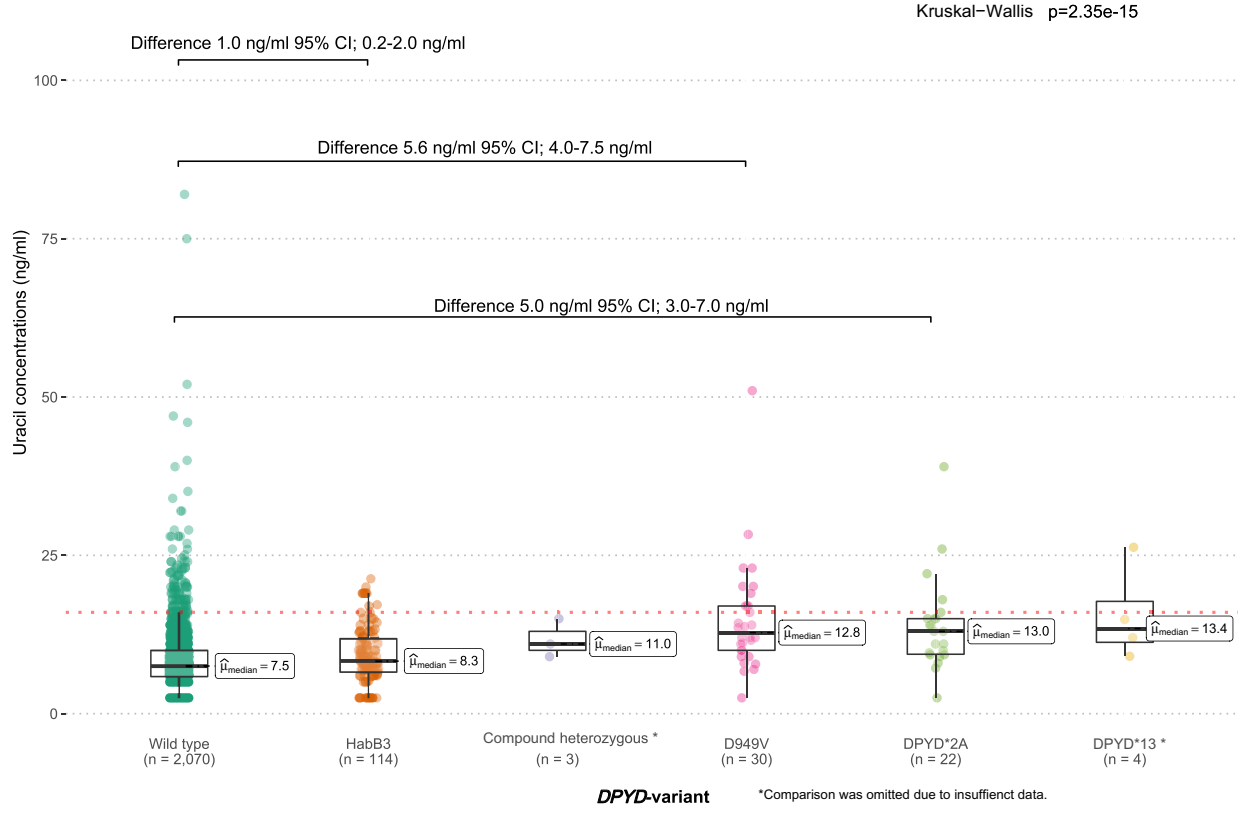

Figure 2. (A) Distribution of uracil concentration between wild type and *DPYD*-variant carriers. (B) The red dotted line represents the cutoff value of 16 ng/mL.

higher since patients with the *DPYD**2 ($n = 18$) variants were excluded before measurements of [U].

Boisdron-Celle *et al.* studied the effect of a multiparametric diagnostic approach in a non-randomized multi-center cohort study with two treatment arms, including 1116 patients [22]. The specific dose recommendations and cutoff values used for FP dosing were not available in the published material, and the authors did not include a comparison between *DPYD*-genotype variants and uracil values. 2.3% (26/1116) of the patients had one of the following *DPYD*-variants: *DPYD**2A, D949V, *DPYD**13. The HapB3 variant was not tested in the study.

De With *et al.* found that among 955 *DPYD* non-carriers treated with FP, pretreatment [U] was not correlated to the rate of severe toxicity (grade $\geq$3) [18]. *DPYD*-variant ($n = 82$) carriers were excluded from this analysis as they received reduced doses of FP. The lack of a correlation between [U] and toxicity was confirmed by comparing [U] to the DPD enzyme activity as measured in peripheral blood mononuclear cells (PMBC) in a subset of 183 patients (*DPYD*-variant $n = 55$, wild type $n = 83$).

As opposed to De Witt [18], we found little between center variance in [U] and none with likely clinical relevance.

The median [U] in *DPYD*-variant carriers was higher than in *DPYD* non-carriers (9.6 ng/mL vs. 7.5 ng/mL; difference 2.5 ng/mL (95% CI 2.0–3.1 ng/mL)), but the strength of the correlation between genotype and [U] was not convincing ($R^2 = 0.15$). This difference does not appear clinically meaningful and does not substantiate either method as clinically useful on a population basis. The poor correlation is in line with other studies comparing [U] across the clinically relevant *DPYD*-variants [18,20,21].

The poor strength of the correlation may be explained to some degree by the *DPYD*-genotyping-test which only includes well-known clinically relevant variants. In the future, more *DPYD*-variants may be included to increase the sensitivity of the genotype test. The normal [U] values in the three compound heterozygous patients could be explained by the SNPs of the two different *DPYD*-variants located on the same allele. The genotyping method used does not determine if the two variants of SNPs are located on the same or different alleles.

The poor performance of the *DPYD*-genotype test indicates that phenotyping using [U] could serve as a reference marker for DPD-activity. Unfortunately, this assumption remains insufficiently substantiated. The evidence supporting the use of [U] and the associated current cutoff values is inadequate; therefore, we cannot conclude that one test is superior to the other. This lack of evidence leaves the clinical oncologist in a complex situation when dosing FP to patients where the two testing methods result conflicting information. e.g., in a patient with normal [U] but a variant *DPYD*-genotype. There is also a risk of underdosing patients with FP if the *DPYD*-genotype is used as the only testing method. De With *et al.* [18] showed that many *DPYD*-variant carriers had normal enzyme activity measured in PMBC, and this underlines the importance of careful dose escalation in patients who tolerate the 50% starting dose of FP.

Our findings substantiate the poor association between genotype and phenotype and reinforce the unmet need for adequately powered prospective clinical trials, including data on toxicity as an outcome to clarify which is the most appropriate test for assessing DPD activity.

Guidelines & clinical practice

Guidelines regarding the use of DPD-testing vary throughout Europe [6,10,23,24]. The latest guideline from the European Society for Medical Oncology (ESMO) regarding colorectal cancer states that DPD testing should be conducted before initiating FP treatment [1].

In France, the phenotype test is the recommended method [6], whereas DPWG recommends the *DPYD*-genotype [10].

In Denmark, the current guidelines suggest that both tests are equal in terms of preemptive dose adjustments. The recommendation is to treat a patient with normal [U] carrying a *DPYD*-variant with a 50% FP starting dose [25].

Strengths

We collected data from all laboratories in Denmark performing DPD-activity testing since the initiation of clinical implementation. The data presented is one of the largest national cohorts comparing clinically relevant *DPYD*-variants with [U] in unselected cancer patients.

Limitations

An explicit limitation of this study is the lack of clinical data regarding the patient's treatment regimen and toxicity. Therefore, we cannot comment on the potential clinical benefit of using DPD-activity testing in Denmark. A clinical study examining the clinical benefit of DPD-testing in Danish cancer patients is ongoing (ClinicalTrials.gov: NCT05266300).

Conclusion

In this Danish population, 7.5% had a clinically relevant *DPYD*-variant, and 5.7% had [U] above the current threshold of $\geq$16 ng/mL. The correlation between *DPYD*-variants and phenotype was poor.

Further clinical studies, including toxicity data, should be performed to compare the safety of FP after dose adjustment according to P-uracil and/or *DPYD*-genotyping.

Disclosure statement

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