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Fluoropyrimidine chemotherapy: recommendations for *DPYD* genotyping and therapeutic drug monitoring of the Swiss Group of Pharmacogenomics and Personalised Therapy

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Summary

Fluoropyrimidines (FPs), mainly 5-fluorouracil (5-FU) and its oral prodrug capecitabine (Cap), remain the backbone of the treatment of many different solid tumors. Despite their broad use in clinical routine, 10–40% of patients experience severe, and in rare cases (0.2–0.5%) even lethal, FP-related toxicity in early chemotherapy cycles. Today, there is a plethora of evidence that genetic variants in the gene encoding for the 5-FU catabolising enzyme dihydropyrimidine dehydrogenase (DPD, encoded by *DPYD*) are predictive of severe FP-related toxicities, and international clinical practice recommendations for *DPYD* genotype-guided FP dosing and therapeutic drug monitoring (TDM) are available. In spite of this strong evidence and *DPYD* genotyping becoming standard practice in other countries, it is has not been widely adopted in Switzerland to date. Here, we discuss current guidelines on genotype-guided FP dosing and TDM, and propose recommendations tailored to the situation in Switzerland to facilitate their clinical uptake for the further individualisation of FP chemotherapy.

We recommend preemptive testing of four *DPYD* variants (c.1905+1G>A (rs3918290), c.1679T>G (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)) in patients with an indication for FP-based chemotherapy, with the costs reimbursed through the compulsory health insurance in Switzerland. Carriers of these variants (6.5% in the Swiss population) have a 40–50% risk of developing severe early-onset toxicity when treated with standard FP doses. In these patients, we therefore recommend the use of a reduced starting dose, based on a dose adjustment scheme provided herein. Furthermore, we recommend the use of infusional 5-FU in patients with a *DPYD* risk genotype in order to enable TDM-based dose escalation. Only if the use of an infusional 5-FU regimen is not feasible should a slow titration of Cap, starting with the recommended reduced dose and basing further doses on monitoring of toxicity, be considered. Given that several studies have shown that TDM in 5-FU treatment improves not only the therapy's safety, but potentially also its efficacy, we also include detailed TDM-based dosing guidelines and discuss the pre-analytical aspects of 5-FU TDM.

Keywords: *fluoropyrimidines*, *5-fluorouracil*, *capecitabine*, DPYD, *therapeutic drug monitoring*, *chemotherapy*, *pharmacogenomics*, *precision medicine*, *guidelines*

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Introduction

The two fluoropyrimidines (FPs) 5-fluorouracil (5-FU) and capecitabine (Cap) are among the most frequently used chemotherapies in the treatment of colorectal, breast, and head and neck cancer [1]. Despite their good performance in diverse treatment settings, the occurrence of severe FP-related toxicities causing severe morbidity or treatment cessation is an important drawback of these drugs. Depending on the treatment regimen, and in particular on the drugs used in combination with the FPs, 10–40% of patients experience severe, and in rare cases (0.2–0.5%) even lethal, FP-related toxicity in early chemotherapy cycles [2–4]. Major toxicity from FP treatment primarily reflects excessive cell death in healthy tissue with rapidly dividing cells, such as the bone marrow and mucous membranes [5]. The most common side effects thus include dose-dependent hematological and gastrointestinal toxicities and skin reactions like hand-foot syndrome (HFS) [6].

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In this context, it is important to note that the toxicity profiles of Cap and 5-FU differ considerably. For example, patients receiving Cap-based therapies have a three-fold higher risk of developing severe HFS [7]. A recently published phase three clinical trial of biliary tract cancer patients treated with Cap reported severe HFS as the most common toxicity (grade ≥3, 20% of patients). This study also reported that around 5% of patients discontinued treatment exclusively due to HFS, even if this toxicity was not life-threatening [8].

A recent study investigated the incidence of FP-related toxicities in France [9]. This study reported that one fifth, 14,700 out of 76,200 patients treated annually with 5-FU or Cap developed serious FP-associated adverse events (SAEs) within the first two cycles of chemotherapy. Gastrointestinal and haematological toxicities were reported as the most common SAEs (66.3%). SAEs were defined in this particular study as "any adverse event entailing hospitalisation or prolongation of hospital stay, permanent disability or invalidity, life-threatening prognosis, and death" [9]. The number of patients with a life-threatening prognosis, disability or death was estimated to be 1200 per year. Adjusting these findings to the Swiss population (France ~65 million vs Switzerland ~8.6 million), around ~2000 FP-related SAEs are expected each year in Switzerland, with life-threatening toxicity, disability or death in approximately 160 patients.

The dose-dependence of FP-related toxicities is demonstrated by clinical studies showing a clear relationship between 5-FU exposure (i.e., area under the curve, AUC) and the severity of FP-related toxicity [10–12], with up to two-fold higher mean 5-FU AUCs observed in patients with life-threatening FP toxicity compared to patients with no or minimal toxicity from 5-FU-based chemotherapy [10].

In current clinical practice, FP dosing is based on a patient's body surface area (BSA), with doses adjusted to meet a prespecified amount of mg/m^2. However, pharmacokinetic studies have demonstrated that BSA-based dosing is very limited in its ability to account for inter-individual differences in FP plasma concentrations [13, 14]. In fact, Gamelin et al. found that systemic 5-FU concentrations vary up to 10-fold between patients receiving BSA-based dosing [14], strongly suggesting an extensive amount of FP pharmacokinetic variability which is not accounted for by BSA. As a result, 5-FU concentrations within the desired therapeutic target range are met only in approximately 15–20% of patients, based on current BSA-guided dosing practices [15, 16]. Several studies have shown the benefit of dose adjustments based on 5-FU plasma levels (therapeutic drug monitoring, TDM) over BSA-dosing, reporting a reduced incidence of FP toxicity, and even evidence for increased efficacy [16–20]. A recently published review of 5-FU TDM, therefore, concluded that TDM is strongly recommended for various 5-FU treatment regimens [21]. However, 5-FU TDM is currently not applied in clinical routine.

Patients with reduced activity of the rate-limiting enzyme for 5-FU catabolism – dihydropyrimidine dehydrogenase (DPD) – are at high risk of supratherapeutic drug concentrations under BSA-based standard dosing, and consequently are at risk of developing severe or sometimes even lethal FP-related toxicities. DPD activity is highly variable in the population [3]. This can be at least partly attributed to genetic variability in its encoding gene, *DPYD*. Specifically, numerous studies have demonstrated the clinical relevance of four genetic variants in *DPYD*, which are predictive for severe FP-related toxicities: c.1905+1G>A (rs3918290), c.1679T>G (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3) [22]. It has also been shown that prospective genotyping of *DPYD* is feasible and even cost-effective [3, 23].

In Switzerland, pharmacogenetic testing of these four *DPYD* risk variants, as well as the measurement of 5-FU plasma levels (TDM), is covered by the compulsory health insurance [24], and analytical procedures have been implemented in clinical diagnostic laboratories [25, 26]. However, in spite of clinical practice recommendations for *DPYD* genotype-based FP dosing and TDM, and their potential for added therapeutic benefit, clinical uptake of these tests has been minimal so far in Switzerland. In the following, we evaluate different guidelines in the context of the current situation in Switzerland, discuss potential reasons for the lack of utilisation in clinical practice, and provide general recommendations for a patient-tailored FP therapy based on pharmacogenetic *DPYD* testing and 5-FU TDM.

The current state of *DPYD* genotyping and TDM

Recently, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) published a recommendation to screen for DPD deficiency in patients before the use of fluoropyrimidines [27]. These recommendations are likely to foster the uptake of *DPYD* genotyping/phenotyping and 5-FU TDM in Europe. Indeed, a consensus position paper in support of the EMA recommendations was published in June 2020 by the German Society for Haematology and Medical Oncology (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie), in cooperation with several societies and groups from Austria, Germany and Switzerland, including the Swiss Society for Medical Oncology (Schweizerische Gesellschaft für Medizinische Onkologie) [28].

Two guidelines to help clinicians interpret *DPYD* genotypes and to adjust the starting FP dose accordingly have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [2, 29]. These two guidelines, in particular those by the CPIC, form the basis of the recent EMA recommendations. However, neither includes 5-FU TDM. A separate guideline addressing the issue of 5-FU-TDM was recently published by Beumer et al. [21].

In some European countries, pre-emptive DPD testing (genetic and/or phenotypic) prior to therapy start is already established in clinical medicine: For example, the Netherlands included *DPYD* genotyping in its "national guidelines for colorectal carcinoma" in 2017. A recently published study reported that by the end of 2018, 87% of FP-treated patients in Amsterdam were tested for DPD deficiency using genotypic and/or phenotypic tests prior to the start of FP therapy [30]. In France, DPD testing is recommended by the National Agency for the Safety of Medicines and Health Products (Agence national de sécurité du médicament et des produits de santé) and laboratory assays

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(genetic and/or phenotypic) are routinely implemented in 17 laboratories across the country [31].

Drug labels are only slowly being updated regarding recent insights into the safety of FP chemotherapy and the benefits of genotype-guided FP dosing, and are currently incomplete: although most current 5-FU and Cap drug labels in Switzerland include and recommend *DPYD* genotyping, they lack information regarding genotype-guided dose adjustments or 5-FU TDM, and do not include the above-mentioned guidelines. Notably, these drug labels also do not fully reflect the current state of the literature regarding other pharmacogenetic markers that are still under investigation in a research context. Specifically, all 5-FU labels contain the outdated information that *TYMS* genotyping (i.e., testing for variants in the gene encoding for thymidylate synthase, the primary therapeutic target of 5-FU chemotherapy) could be beneficial in predicting toxicity to 5-FU-based chemotherapy. However, no prospective evidence for the clinical relevance of these pharmacogenetic markers with regard to 5-FU toxicity currently exits [32] (table 1). Such outdated information may lead to confusion and hamper the clinical implementation of *DPYD* genotyping and TDM in order to further individualise FP dosing.

Preemptive *DPYD* genotyping

Both available guidelines (CPIC and DPWG) highlight the four *DPYD* risk variants (c.1905+1G>A (rs3918290), c.1679T>G (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)), as these have the strongest evidence regarding their impact on DPD activity and FP toxicity risk [2, 29] (table 2). All four variants have been consistently associated with severe FP-related toxicity and impaired DPD activity. Two of these variants (c.1905+1G>A (rs3918290), c.1679T>G (rs55886062)) lead to alleles producing an enzyme with only minimal or no residual activity, termed "no function" alleles according to the CPIC functional classification. The other two variants (c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)) have a less severe effect on DPD activity and are termed "decreased function" alleles. In patients carrying one copy of these two variants, DPD activity in peripheral blood cells is reduced by 31-34% and 20-35% respectively, whereas this reduction in activity is approximately 45-68% for the two "no function" variants [3, 33]. The combined carrier frequency of *DPYD* risk variants in the Swiss population is about 6.5%, which means that one out of every 15 patients carries at least one such variant [4].

Both guidelines translate genotypes into an enzymatic activity score to derive dosing recommendations based on the *DPYD* genotype. Briefly, normal function alleles are assigned a value of one, "decreased function" alleles a value of 0.5, and "no function" alleles a value of zero. The DPD phenotype is subsequently assigned using a gene activity score, calculated as the sum of the two lowest allele function scores. For heterozygous carriers of the four *DPYD* risk variants described above, the gene activity score is thus 1.5 for c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3) and one for c.1905+1G>A (rs3918290) and c.1679T>G (rs55886062).

In spite of the varying severity of their impacts on DPD activity and the resulting differing gene activity scores, both guidelines currently recommend a 50% dose reduction for all heterozygous carriers of one of these variants. This recommendation is primarily based on a recent prospective study where a 25% reduction in the initial FP dose in heterozygous carriers of the "decreased function" variants was not sufficient to reduce the rate of early-onset FP-related toxicity to that observed in patients with no risk variants, while a 50% dose reduction achieved this goal for the two "no function variants" [3, 23].

While the guidelines are in agreement with respect to dose recommendations for heterozygous carriers of a single

Table 1: Overview of information on fluoropyrimidine pharmacogenetics and therapeutic drug monitoring in Swiss 5-fluorouracil and capecitabine drug labels.

Drug	Update	Includes DPD deficiency	Includes *DPYD genetic* variation	Recommends testing for *DPYD* risk variants	Provides dosing recommendation	Includes therapeutic drug monitoring	Includes *TYMS* genotyping*
Fluorouracil Accord†	Jul 20	+	+	+	–	–	+
Fluorouracil Labatec‡	Apr 19	+	+	+	–	–	+
Fluorouracil Sandoz§	Jul 20	+	+	+	–	–	+
Fluorouracil Teva¶	Jul 20	+	+	+	–	–	+
Xeloda‖	Aug 20	+	+	+	–	–	–

* *TYMS* encodes for thymidylate synthase enzyme, which is the primary target of 5-FU chemotherapy. Several studies showed only a moderate effect of *TYMS* variants on the development of fluoropyrimidine-related toxicities. No prospective study has shown the usefulness of *TYMS* markers as toxicity predictors. † Accord Healthcare AG; ‡ Labatec Pharma SA; § Sandoz Pharmaceuticals AG; ¶ Teva Pharma AG; ‖ Roche Pharma (Schweiz) AG Drug labels were retrieved from https://www.swissmedicinfo.ch/?Lang=EN and last accessed on 19 Sept 2020.

Table 2: *DPYD* risk variants.

DPYD variant	Carrier frequencies		Biological effect
	Swiss population	EU population	
c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)	4.7%	4.1%	Decreased function allele (affects mRNA splicing)
c.2846A>T (rs67376798)	0.6%	1.0%	Decreased function allele (affects co-factor binding Asp949Val)
c.1679T>G (rs55886062)	0.4%	0.1%	Nonfunctional allele (affects protein stability Ile560Ser)
c.1905+1G>A (rs3918290)	0.8%	1.0%	Nonfunctional allele (affects mRNA splicing)

Frequencies for Swiss population are from Froehlich et al [4]. Frequencies for the EU population were retrieved from gnomAD database (European non-Finnish).

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DPYD risk variant, which constitute the vast majority (>98%) of risk variant carriers, they differ for rare homozygous or compound heterozygous carriers (table 3). The CPIC guidelines recommend a 50% dose reduction in patients homozygous or compound heterozygous for any of the two "decreased function" alleles and the use of alternative, non-FP-based chemotherapy in patients compound heterozygous for different combinations of a "no function" and a "decreased function" allele (table 3). The DPWG guidelines, on the other hand, recommend the measurement of DPD activity in peripheral blood cells in these patients and an FP dose adjustment corresponding to the measured enzyme activity. Both guidelines recommend against the use of FP-based chemotherapy in patients who are homozygous or compound heterozygous for the two "no function" alleles (table 3). It is important to note that among Swiss patients, carriers of more than one of the four risk variants are expected to be very rare (~1 in 1000), and clinical data on patients carrying these genotypes is very limited. For this reason, activity scores for combinations of multiple *DPYD* risk variants are mostly extrapolated from data based on carriers of a single risk variant.

Another discrepancy between these guidelines is that the CPIC does not give any recommendation on tegafur due to limited evidence, whereas the DPWG includes dose recommendations for tegafur. Since tegafur is not available in Switzerland, we do not consider it in this review.

Currently, all existing guidelines advise against FP treatment in homozygous carriers of no function *DPYD* alleles due to a lack of data. Although it was shown for a single case that treatment with extremely low FP doses in is principle feasible, the therapeutic effectiveness of such a low-dose treatment is unknown [34].

Limitations of *DPYD* genotyping

A common criticism of preemptive *DPYD* genotyping is its low sensitivity, i.e. the considerable inter-individual variability in FP exposure and FP toxicity that is not fully explained by the four well-studied *DPYD* risk variants [2, 29]. These variants explain only approximately 20% of the severe toxicities (grade ≥3) in patients of Caucasian origin. However, when considering life-threatening toxicities (grade 4–5 toxicity within the first 12 weeks of treatment), a systematic review of 6403 patients revealed that 29.3% of the 518 severe toxicity cases were carriers of one of the four *DPYD* risk variants [35]. Importantly, preemptive genotyping in the Netherlands has been shown to reduce overall treatment costs due to reduced costs related to the management of adverse events even when only a proportion of severe toxicities can be prevented with this pharmacogenetic test [36].

A second concern regarding the implementation of preemptive *DPYD* pharmacogenetic testing is the potential risk of underdosing patients when using reduced initial doses, and thereby impairing the treatment efficacy of these drugs. This concern is based on the observation that about half of patients carrying *DPYD* risk variants tolerate standard doses [3, 23]. To address this concern, the CPIC guidelines recommend dose titration based on TDM or tolerable toxicities in order to maintain treatment efficacy [2, 37].

There are also some concerns regarding potential treatment delays caused by pre-treatment *DPYD* genotyping. As neither 5-FU nor Cap is used for oncological emergencies, a turnaround time of five working days is adequate. Targeted genotyping of the four well-established *DPYD* risk variants can be performed sufficiently quickly with standard equipment available in diagnostic genetic laboratories in Switzerland. Furthermore, delays due to prolonged sample transport time are of no concern in Switzerland given the highly developed transportation services which allow the overnight delivery of samples if necessary.

Furthermore, genotyping only these four most common *DPYD* risk variants means that other, rarer *DPYD* variants cannot be ruled out. However, the cumulative frequency of all other deleterious *DPYD* mutations known to date is <0.1% in Europeans. Thus, it is estimated that these extremely rare deleterious variants can only explain a small additional fraction of all occurrences of severe toxicity [38], making targeted genotyping a pragmatic approach in these populations. Importantly, most data currently available on *DPYD* variation and FP-related toxicity is based on studies in Caucasian populations, and additional variants may occur at higher frequencies in patients of other ethnicities. Indeed, an additional "decreased function" variant, c.557 A>G (rs115232898, p.Y186C), has a frequency of 2.1% in African and African American populations [39]. Unfortunately, due to its size, current technologies do not allow resequencing of the entire *DPYD* gene in a time- and cost-efficient manner for wide clinical implementation. However, resequencing all of *DPYD*'s protein-coding sequences might become feasible in the near future, and can already be used today in special cases. This has the potential to further increase the sensitivity of *DPYD* genotyping [40], albeit only to a limited extent and particularly in patients of non-Caucasian or mixed ancestry [2]. For such cases, the CPIC guidelines include curated allele function

Table 3: Fluoropyrimidine dosing recommendations according to *DPYD* genotype.

***DPYD* genotype**		**Recommended starting dose in %**		
		CPIC	**DPWG**	**SPT**
Heterozygous for a single DPYD risk allele	e.g., c.2846A>T/= or c.1905+1G>A/=	50%	50%	50%†
Two decreased function alleles	e.g., c.2846A>T/c.2846A>T or c.1129-5923C>G/c.2846A>T	50%	PHENO*	25%†
One decreased function -and one nonfunctional allele	e.g., c.1905+1G>A/c.1129-5923C>G or c.2846A>T/c.1679T>G	0%	PHENO*	0%
Two nonfunctional alleles	e.g., c.1905+1G>A/c.1905+1G>A or c.1679T>G/c.1905+1G>A	0%	0%	0%

5-FU = 5-fluorouracil; CPIC = Clinical Pharmacogenetics Implementation Consortium; DPWG = Dutch Pharmacogenetics Working Group; SPT = Swiss Group of Pharmacogenomics and Personalised Therapy; TDM = therapeutic drug monitoring * Requires further assessment by DPD phenotyping; † use infusional 5-FU followed by TDM-based dose titration

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definitions for many rare and non-Caucasian variants to enable the calculation of activity scores and dosing recommendations. It is worth noting that genetic variants in other FP-metabolising genes have also been shown to be associated with FP-related SAEs, which might explain further toxicity cases. However, these variants require further research in order to be implemented as clinical markers [41].

DPD phenotyping

Given the substantial residual variability in DPD activity even among patients with identical risk variant genotypes, several approaches for direct phenotyping of DPD activity have been investigated as potential predictors for FP-related toxicities [42]. As mentioned above, the DPWG guidelines recommend the measurement of DPD activity in peripheral blood cells in patients with certain *DPYD* genotype combinations (table 3). However, none of the phenotyping methods evaluated so far have a comparable strength of evidence supporting their predictive power for severe FP-related toxicity as is available for *DPYD* genotyping. The sensitivity and specificity of these assays have not been clearly established, they are not as easily standardised between laboratories as a genotyping test, and some are also labor-intensive and logistically challenging. For this reason, no general cut-offs or dosing recommendations based on DPD phenotyping have been established, and to our knowledge no clinically validated phenotyping assay is currently available in Switzerland. While such assays may become important in the future as complementary methods to *DPYD* genotyping, no phenotyping approach can be recommended at this point [41].

5-FU TDM: practical considerations

In a majority of patients, BSA-based FP dosing results in drug concentrations below the therapeutic range, suggesting significant potential for added therapeutic benefit with improved FP dosing tailored towards the individual requirements of each patient. The traditional practice of escalating the dose of 5-FU in patients experiencing no or low toxicity in the previous cycle [43] has been largely abandoned in recent times because this clinician-based dosing is difficult to reproduce and could not be implemented in the latest generation of trials. Indeed, several studies have demonstrated the superiority of pharmacokinetics-guided 5-FU-dosing both in relation to treatment effectiveness and toxicity [16–20]. In the light of this strong evidence, the recently published comprehensive review on 5-FU TDM by Beumer et al. concludes that TDM is strongly recommended in all patients treated with various 5-FU treatment regimens [21]. The established target range for continuous 5-FU infusion, determined based on a balance between therapeutic benefit and toxicity, is an AUC of 20–30 mg×h/l. However, this target range is not recommended for bolus only regimens and infusion durations of over 120h. The review concludes that the following 5-FU regimens should include TDM: "FOLFOX4, FOLFOX6, FOLFOX7, FOLFIRI, LV5FU, FUFOX, AIO, weekly 1.5g/m^2/8 hours for CRC and 1.0g/m^2/ day D1–4 or 1.0g/m^2/day D1–5 for SCCHN" [21]. Importantly, this recommendation only applies to therapies with infusional 5-FU, whereas the utility of TDM in Cap-based regimens is not clearly established. Cap is converted to 5-FU in cancer and some non-neoplastic cells; consequently, the plasma exposure of 5-FU is very low [44]. At present, the correlation of plasma concentrations of Cap or its metabolites with clinical outcomes (effectiveness, toxicity) is unclear, and therapeutic target ranges have not been defined. As a result, TDM cannot be used to adjust dosing for Cap-based regimens.

Assays for measuring 5-FU plasma concentrations to determine the AUC of infusional 5-FU therapies are available in Switzerland. For example, a high-performance liquid chromatography–mass spectrometry method for measuring 5-FU in plasma was developed by Büchel et al. [26]. Commercial assays are also available and have been implemented in diagnostic laboratories [25]. However, 5-FU TDM is currently hampered by pre-analytical challenges [21]. 5-FU is rapidly catabolised after blood collection by DPD enzyme, which is present in blood cells. Therefore, rapid centrifugation or the immediate addition of a stabilising agent, a DPD inhibitor, is required. Improper sample preservation can cause falsely low 5-FU concentration measurements, which could lead to overdosing of the patient in the following cycles. In the case of a suspected false low result, a repeated measurement in the next therapy cycle is therefore suggested prior to any dose-adjustment. Another limitation is the inaccuracy of the run time of infusion pumps for 5-FU. This was illustrated by a study reporting high variability in 5-FU drug delivery using elastomeric pumps [45]. While electronic infusion systems might improve the accuracy of drug delivery, they carry the risks of false programming and free flow. They are also more labour- and cost-intensive [46, 47]. But most importantly, the electronic devices are less convenient and reassuring for the patient than the "connect and forget" elastomeric pumps. In 2010, the FDA launched the Infusion Pump Improvement Initiative, recognising the need to address issues associated with the different types of pumps [48]. Calculation of the 5-FU AUC based on a single time point requires a steady-state drug concentration measurement, taken when the pump is delivering the drug at a constant rate during the continuous infusion. If the blood draw is taken too close to the expected end of the infusion time, it is not uncommon that the pump is already empty, and thus the measured drug concentration no longer reflects the steady state, making any PK assessment impossible. To avoid uninterpretable measurements, it is therefore recommended that the blood collection is scheduled with sufficient time prior to the planned end of the infusion (e.g., after 24–36 hours for 48-hour infusions), which in many cases requires an additional office visit by the patient. An early blood draw close to the therapy start is not recommended since it has been shown that the steady-state level of 5-FU is not reached after two hours of infusion [49]. Importantly, blood must be drawn from a separate venipuncture and not from the infusion port, as this will lead to falsely high results, even if the port is washed several times [21]. Based on current evidence, we agree with the guideline recommendation [21] that 5-FU TDM would be beneficial in all patients treated with this drug. However, the limitations of the infusion pumps in current use and pre-analytical difficulties may impair the general implementation of 5-FU TDM in clinical routine. Therefore, we recommend 5-FU TDM specifically in patients carrying a *DPYD* risk variant and in whom starting doses are reduced based on this genotype so as to minimise the risk of underdosing.

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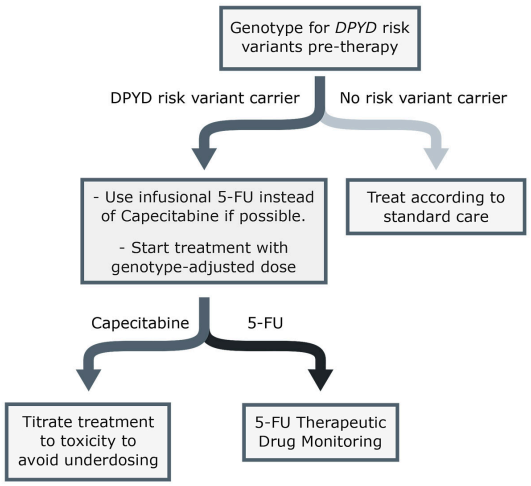

Figure 1: Simplified scheme for fluoropyrimidine dosing. 5-FU = 5-fluorouracil.

We provide a dosing scheme in table 4, which was adapted from Kaldate et al. [49]. In order to fully recommend 5-FU TDM in every patient, infusion pumps with more accurate run times and less error-prone pre-analytical procedures are required.

SPT recommendations

In brief, we strongly recommend *DPYD* genotyping of the four *DPYD* risk variants (c.1905+1G>A (rs3918290), c.1679T>G (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182, c.1236G>A/HapB3)) prior to the start of therapy, followed by a reduction of the initial dose to 50% of the standard dose in patients who are heterozygous carriers of one of these variants, as recommended in the CPIC guidelines [2]. In order avoid unnecessary treatment delays, it is advisable to include the date of treatment start when submitting samples for *DPYD* genotyping; genotyping results should be reported within five working days after receipt of the samples by the laboratories. Our recommendations are summarised in figure 1. A more detailed scheme is shown in figure S1 in appendix 1. While we generally recommend following the CPIC guidelines, we propose the following adjustments or additions:

1. We recommend the use of a starting dose of 25% of the standard dose in carriers of two decreased function alleles, instead of the 50% starting dose recommended in the CPIC guidelines [2] (table 3). Due to a lack of scientific evidence, our more conservative recommendation is based on a consensus opinion of our working group. Cases of patients who are homozygous for the decreased function allele c.1129-5923C>G (rs75017182, c.1236G>A/HapB3) experiencing lethal toxicity in early cycles when treated with standard 5-FU doses have been reported [4], as has a DPD activity of only 10% in a homozygous carrier of c.2846A>T [50]. Given these observations, it is not clear whether the effects of rare compound heterozygous and homozygous genotypes can be linearly extrapolated based on allele scores derived from heterozygous carriers, and so a more conservative dosing strategy is warranted.
2. In patients carrying a *DPYD* risk variant, dose titration based on TDM should be favoured over toxicity-based dose titration. While dosing algorithms for TDM-based dose adjustments are available [49], no similar algorithms have been validated for dose escalation based solely on the monitoring of toxicity.
3. To enable TDM-based dose titration, we generally recommend treating patients carrying a *DPYD* risk variant with an infusional 5-FU regimen and avoiding the use of the oral prodrug Cap. Only if the use of an infusional 5-FU regimen is not possible, should a prudent titration of Cap doses based on monitoring of toxicity and starting with the recommended reduced dose be considered, i.e., as stated in the CPIC guideline: "Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy or decrease the dose in patients who do not tolerate the starting dose to minimise toxicities." Interestingly, case reports are available from *DPYD* risk variant carriers who experienced severe toxicity with standard dosing of a Cap-based regimen but subsequently tolerated standard doses of infusional 5-FU after slow dose titration [51]. We have knowledge of similar cases in Switzerland through our diagnostic services (C.Largiadèr, U.Amstutz, personal communication).
4. Pre-treatment genotyping of the four *DPYD* risk variants can detect >98.5% of carriers of risk alleles in this gene among patients of Caucasian ancestry. Patients with non-Caucasian origins might benefit from *DPYD* sequencing, which is available in Switzerland in specialised laboratories [4]. Alternatively, a targeted genotyping method that includes additional "decreased

Table 4: 5-fluorouracil TDM dosing scheme.

5-FU AUC (mg×h/l)	Dose adjustment in the next cycle in %
>40	30% lower
37–39	25% lower
34–36	20% lower
31–33	10% lower
20–30	No change required
17–19	10% higher
14–16	20% higher
8–13	25% higher
<8	Repeat the previous dose to exclude possible pre-analytical errors. If repeated AUC <8, dose adjustment: 30% higher

5-FU = 5-fluorouracil; AUC = area under curve; TDM = therapeutic drug monitoring This dosing scheme is adaptated from Kaldate et al. [46]

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function" or "no function" *DPYD* variants known to occur at similar frequencies as the four primary risk variants in other ethnicities could be used.

Disclosure statement

The authors declare no potential conflicts of interest.

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Appendix 1: Supplementary figure

Figure S1: SPT guideline for fluoropyrimidine dosing.

The appendix is available as a separate file at: https://smw.ch/article/doi/smw.2020.20375.

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