

# DPD: 5-fluorouracil/capecitabine

# 2551/2552/4893/4894/ 6192

95% CI = 95% confidence interval, AS = gene activity score, AS 0 = gene activity score 0 = two non-functional alleles (\*2A/\*2A, \*2A/\*13 or \*13/\*13) or more general two gene variants leading to non-functional alleles (\*2A-homozygosity, \*13-homozygosity, or both \*2A and \*13), AS 1 = gene activity score 1 = one fully functional and one non-functional allele (\*1/\*2A or \*1/\*13), AS 1.5 = gene activity score 1.5 = one fully functional and one partially functional allele (\*1/1236A or \*1/2846T), AS 2 = gene activity score 2 = two fully functional alleles (normal metaboliser; \*1/\*1), CAP = capecitabine, CI = clearance, comb = combination therapy ( $\geq$  2 oncolytic drugs), C<sub>ss</sub> = steady-state plasma concentration, DPD = dihydropyrimidine dehydrogenase, FENO = fenotyping = two partially functional alleles (1236A/1236A, 1236A/2846T or 2846T/2846T) or one non-functional and one partially functional alleles (1236A-homozygo-sity, 2486T-homozygosity, or both 1236A and 2846T) or a gene variant leading to a non-functional allele and a gene variant leading to a partially functional allele (\*2A plus 1236A, \*2A plus 2846T, \*13 plus 1236A or \*13 plus 2846T), FU = fluorouracil, mono = monotherapy (1 oncolytic drug), NS = non-significant, OR = odds ratio, OR<sub>adj</sub> = adjusted odds ratio, RR = relative risk, RR<sub>adj</sub> = adjusted relative risk, S = significant, SmPC = Summary of Product Characteristics, SNP = single nucleotide polymorphism

**Disclaimer:** The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

# Brief summary and justification of choices:

5-Fluorouracil is mainly (> 80%) converted by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites. Lower metabolic activity of DPD leads to increased intracellular concentrations of fluorodeoxyuridine monophosphate, the active metabolite of 5-fluorouracil and its prodrug capecitabine. This increases the risk of toxicity due to overdosing such as neutropenia, thrombopenia and diarrhoea.

18 of 20 studies and all 3 meta-analyses found an increased risk of grade  $\geq$  3 toxicity (either global or at least one specific kind of toxicity) for patients with gene variants resulting in reduced DPD activity (gene activity score (AS) 0 to 1.5 and fenotyping (FENO)). This increased risk was shown separately for AS 1 and 1.5, but AS 0 and FENO, were only investigated combined with other genotypes. However, both the stronger deficiency of these latter genotype groups and the development of severe toxicity in cases, confirm that the risk is also increased for AS 0 and FENO. In one study investigating response, there was no effect of gene variants. Because of the increased toxicity risk, the working group concludes that gene-drug interactions are present and that they necessitate therapy adjustment (yes/yes-interactions).

The recommended therapy adjustment per genotype group and the justification for these adjustments are indicated below.

#### Recommended therapy adjustments

Dose adjustments have been calculated on the basis of 5-fluorouracil clearance or AUC, also for patients receiving capecitabine. In addition, titrated doses and residual DPD enzyme activities are taken into account. Data on 5-fluorouracil clearance or AUC are only available for \*1/\*2A, \*1/2846T and \*2A/2846T. There are data from one patient with \*1/\*13 who developed severe toxicity on 5-fluorouracil, from one patient with 2846T/2846T and from one patient with 1236A/2846T.

AS 1.5: For \*1/2846T, the weighted average of the calculated dose adjustments was a reduction to 55%. However, Deenen 2011 investigated 8 patients with \*1/2846T and found a toxicity-guided dose reduction to 76% of the standard dose. In addition, Lunenburg 2016 found no grade ≥ 3 toxicity when treating five patients with \*1/1236A with an initial dose of 75% of the standard dose. Deenen 2011 did not find significantly more dose decreases for \*1/1236A + 1236A/1236A compared to \*1/\*1 when treating 568 patients with chemotherapy with capecitabine 1000 mg/m<sup>2</sup> twice daily. Kleinjan 2019 found the tolerated dose for 6 patients with \*1/1236A to be 78% of the normal dose. The single patients with \*1/2846T in Lunenburg 2018 and Kleinjan 2019 tolerated 60% and 85% of the normal dose, respectively. In a study with 51 patients with \*1/1236A and 17 patients with \*1/2846T, Henricks 2018 Lancet Oncol found the titrated dose to be 74% of the normal dose for \*1/1236A and 64% for \*1/2846T. The mean and median DPD enzyme activity in this study were respectively 80% (standard deviation 30%) and 74% of that for \*1/\*1 for \*1/1236A, and respectively 66% (standard deviation 20%) and 67% for \*1/2846T. In this study, the (planned) starting dose was 75% of the normal dose, but bad tolerance was induced in 6% of patients with \*1/1236A by increasing the dose afterwards and in 12% of patients with \*1/2846T, either by not applying a reduced starting dose or by increasing the dose after tolerance for the reduced starting dose. In this study, the percentage of patients with overall grade  $\geq$  3 toxicity was still higher for \*1/236A and for \*1/2846T on (planned) reduced starting dose than for \*1/\*1 on the normal starting dose. To avoid this additional toxicity in patients with \*1/1236A and \*1/2846T, the KNMP Pharmacogenetics Working Group recommends starting with a lower than the calculated dose (i.e. 50% instead of 75% or 65% of the normal dose) and subsequently adjust the dose based on toxicity and efficacy.

Instead of dose adjustment, physicians may also choose an alternative.

For 25x \*1/\*2A and 1x \*1/\*13, the weighted average of the dose adjustments calculated based on 5-fluoro-AS 1: uracil clearance or AUC was a reduction to 47% (20-49%, median 46%) (Deenen 2016, Bois-dron-Celle 2007 and Morel 2006). The weighted mean of 47% was translated to 50% to be more achievable in clinical practice. Several studies on tolerated doses, residual enzyme activities and a 50% starting dose for AS 1 support this dose recommendation. Titrated or tolerated doses were 56% of the normal dose in Deenen 2011 (n = 5), 61% in Van Kuilenburg 2012 (n = 9), < 50% in Magnani 2013 (n = 3), 48% in Deenen 2016 (n = 18), 53% in Lunenburg 2016 (n = 4), 57% in Henricks 2018 Lancet Oncol (n = 17) and 54% in Kleinjan 2019 (n = 4). DPD enzyme activities were 64% of that for 1/1 in Deenen 2016 (n = 15) and 54% in Henricks 2018 Lancet Oncol (n = 9; standard deviation for \*1/\*2A of 8% (n = 8); median 56% (n = 8)). In addition, Henricks 2018 Int J Cancer found no differences in toxicity and efficacy between 40 \*1/\*2A-patients (37 for efficacy) on a starting dose of approximately 50% of the normal dose and \*1/\*1-patients on the normal dose. Henricks 2018 Lancet Oncol found no differences in toxicity between 17 patients with AS 1 on a starting dose of 50% of the normal dose and \*1/\*1-patients on the normal dose, despite bad tolerance being induced by a subsequent dose increase in 12% of the patients with AS 1. Deenen 2016 found no difference in toxicities between 18 patients with \*1/\*2A on an initial dose of maximally 50% of the normal dose and \*1/\*1-patients on the normal dose. Lunenburg 2016 found no grade  $\geq$  3 toxicity when treating three patients with \*1/\*2A with an initial dose of 50% of the normal dose.

Based on these data, the KNMP Pharmacogenetics Working Group recommends to start with 50% of the normal dose. If appropriate, the dose can subsequently be adjusted based on toxicity and efficacy. Instead of dose adjustment, physicians may also choose an alternative.

Clearance has only been determined for one patient with genotype \*2A/2846T (Boisdron-Celle 2007). The FENO: clearance found for this patient was almost zero. For 1x 2846T/2846T and 1x 1236A/2846T, the average of the dose adjustment calculated based on 5-fluorouracil AUC was a reduction to 19% (12% for 2846T/2846T and 44% for 1236A/2846T) (Henricks 2017). Data on titrated or tolerated doses and on residual DPD enzyme activity showed a similar high range in values, both within as between the different genotypes. For 5 patients with 1236A/1236A, the tolerated dose varied from 40% to 100% of the normal dose (Meulendijks 2016 and Henricks 2017). For one patient with 2846T/2846T, the tolerated dose was 17% of the normal dose (Henricks 2017). For one patient with both 1236A and 2846T, the tolerated dose was 51% of the normal dose (Henricks 2017). For 4 patients with 1236A/1236A, the DPD enzyme activity varied from 41% to 79% of the activity in patients without a gene variant (Meulendijks 2016 and Henricks 2017). For 2 patients with 2846T/2846T, the DPD enzyme activity varied from 10% to 29% of the normal value (Henricks 2017). For one patient with both 1236A and 2846T, the DPD enzyme activity was 45% of the normal value (Henricks 2017). Lunenburg 2018 Genes (Basel) found 2 patients with gene activity 0.25-0.5 with null allele to tole-rate 50% of the normal dose. These patients had respectively 60% and 72% of the normal DPD enzyme activity. However, 4 patients with this phenotype who had previously developed sever toxicity on full dose fluoropyrimidines had DPD enzyme activities ranging from 1% to 38% of the normal value. The low DPD enzyme activities in these patients might be due to neutropenia, because DPD enzyme activity is measured in mononuclear cells. So in these 6 patients, the DPD activity was 33% of that measured in \*1/\*1patients, but 66% if measured prior to toxicity.

Because of the high interpatient variability, the scarcity of data for calculating a dose recommendation, and the low prevalence of patients with two gene variants (0.35% of the 1138 genotyped patients in Henricks 2018 Lancet Oncol), the KNMP Pharmacogenetics Working Group recommends to fully personalise therapy in these patients, i.e. measure DPD enzyme activity and adjust the fluoropyrimidine dose accordingly. Instead of dose personalisation, physicians may also choose an alternative.

AS 0: There are not enough data to be able to make a substantiated recommendation on dose adjustments for gene activity 0. The recommendation for \*1/\*2A is a dose reduction by 50%. This would be equivalent to a dose reduction by 100% for \*2A/\*2A and therefore a dose reduction to 0. This agrees with the severe toxicity found in one patient with genotype \*2A/\*2A when using 5-fluorouracil cream on the scalp. Because of the indications that the tolerated dose is close to zero and the scarce data on tolerated doses in patients with gene activity 0 (see below), an alternative is recommended.

The calculated dose reduction based on 2 patients is a reduction to 0.81% of the normal dose (0.72-0.89%; median 0.81%). However, this is based on too few patients to be used for a substantiated dose

recommendation. In addition, in one of these patients, having undetectable DPD activity, the dose had to be reduced from 0.65% to 0.43% of the normal dose during treatment. However, there is a fairly good correlation between the residual DPD enzyme activity in peripheral blood mononuclear cells and the tole-rated dose (Meulendijks 2016, Deenen 2016, Henricks 2017 and Henricks 2018 Int J Cancer, Henricks 2018 Lancet Oncol and Lunenburg 2018 Genes (Basel)). Therefore, if an alternative is not possible, adjusting the dose according to the residual DPD enzyme activity in peripheral blood mononuclear cells is recommended. This strategy has been shown to be feasible in two patients with gene activity 0. A patient with 0.5% of the normal DPD activity tolerated 0.8% of the normal dose (150 mg capecitabine every 5 days) (Henricks 2018 Int J Cancer). A patient with undetectable DPD activity, tolerated 0.43% of the

normal dose (150 mg capecitabine every 5 days with every third dose skipped) (Henricks 2017). You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

#### Recommendation concerning pre-emptive genotyping, including justification of choices:

#### Capecitabine and systemic fluorouracil

The Dutch Pharmacogenetics Working Group considers genotyping before starting systemic fluorouracil or capecitabine to be essential for drug safety. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 8 out of the maximum of 10 points (with pre-emptive genotyping considered to be essential for scores ranging from 6 to 10 points):

The risk of serious life-threatening toxicity is increased for patients with a genotype resulting in diminished DPD enzyme activity (gene activity scores 0-1.5 and fenotyping). This toxicity can be fatal (grade 5). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the genedrug interaction (2 points for CTCAE grade 5).

The increased risk for serious life-threatening toxicity (code E corresponding to grade 4) has been shown in 18 studies and 3 meta-analyses. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade  $\geq$  3 (3 points for three or more publications with level of evidence score  $\geq$  3).

The number needed to genotype was deduced from two articles on a large Dutch study to be 163. Deenen 2016 found 18 \*1/\*2A in 1631 patients. Based on historical data, 73% of \*1/\*2A and 23% of non-genotyped patients (predominantly \*1/\*1) would have developed grade  $\geq$  3 toxicity on full dose fluoropyrimidine. This corresponds to 9 additional patients with toxicity. Meulendijks 2017 found 19 carriers of 2846T, 3 carriers of \*13 and 58 carriers of 1236A in 1606 of the 1615 \*2A-negative patients. The positive predictive value for grade  $\geq$  3 toxicity in the first cycle was 13% for all 3 gene variants combined. The negative predictive value was 88%, indicating that 12% of patients without a gene variant developed grade  $\geq$  3 toxicity in the first cycle. This corresponds to 1 additional patient with toxicity (1% of the 80 gene variant carriers). Thus the number needed to genotype to prevent a patient developing grade  $\geq$  3 toxicity risk in these patients, so that the deduced number to genotype indeed reflects the number of patients to genotype to prevent one case of grade  $\geq$  3 toxicity as treatment of \*1/\*1 with the normal initial dose. The calculated number to genotype of 163 results in 1 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade  $\geq$  3 (1 point for 100  $\leq$  NNG  $\leq$  1000).

The Summary of Product Characteristics (SmPC) of capecitabine indicates that capecitabine is contra-indicated in patients with complete DPD deficiency (corresponding to gene activity score 0). This results in the maximum number of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for at least one genotype/phenotype mentioned as a contra-indication in the corresponding section). In addition to the clinical implication score indicating pre-emptive genotyping to be essential, three cost analyses suggest that the costs for genotyping of all patients are less than the costs of treating the additional patients with toxicity if genotyping is not performed (Henricks 2019, Cortejoso 2016 and Deenen 2016). Thus, pre-emptive genotyping might not only be essential, but also cost-saving.

# Cutaneous fluorouracil

The Dutch Pharmacogenetics Working Group considers genotyping before starting cutaneous fluorouracil to be potentially beneficial for drug safety. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline. The clinical implication of the gene-drug interaction scores 2 out of the maximum of 10 points (with pre-emptive geno-typing considered to be potentially beneficial for scores ranging from 0 to 2 points):

The literature reports only one case of a patient with gene activity score 0 (\*2A/\*2A) developing toxicity code D, corresponding to grade 3, when treated with fluorouracil cream. This results in a score of 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE grade 3 or 4). In addition, it results in a score of 0 of the maximum of 3 points for the second crite-

rion of the clinical implication score, the level of evidence supporting the associated clinical effect grade  $\geq$  3 (only points for at least one publication with level of evidence score  $\geq$  3).

In the Netherlands, the frequency of \*2A is 0.6% and the frequency of \*13 0.1%. This indicates, that even if all compound heterozygotes for these variants have the variants on different alleles, the prevalence of gene activity score 0 is only 1 out of 20.408. Thus, more than 20.000 patients should be genotyped to find 1 patient with an increased risk. In addition, it is not known how large the risk is for this patient, because only one case has been reported, Thus, it can only been concluded that the number needed to genotype to prevent one clinical effect grade  $\geq$  3 is more than 20.400. This results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade  $\geq$  3 (no points for NNG > 1000).

The Dutch Summary of Product Characteristics (SmPC) of fluorouracil cream contains a warning for a possible risk of severe systemic toxicity in patients with a defective DPD enzyme. However, it does not contain a recommendation to genotype, nor does it mention a genotype/phenotype as a contra-indication. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype being mentioned in the SmPC in the absence of a recommendation to genotype and/or a genotype/phenotype being mentioned as a contra-indication in the corresponding section).

The table below follows the KNMP nomenclature for the gene variants. The nomenclature for the gene variants used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 – CAP,	3	11 patients, heterozygous for a gene variant, received capeci-	Authors' conclusion:
mono/comb		tabine treatment with reduced doses (75% of the normal dose	'Tolerance-based
Kleinjan JP et al.		for gene activity 1.5 and 50% of the normal dose for gene acti-	capecitabine dose
Tolerance-based		vity 1), that were subsequently adjusted on basis of tolerance	escalation did not
capecitabine dose		according to a prespecified protocol. Only patients receiving	lead to more toxicity
escalation after		capecitabine mono- or combination therapy without radiation	in DPYD variant
DPYD genotype-		and completing at least one treatment cycle were considered.	carriers compared
guided dosing in		Capecitabine doses according to protocol (normal doses)	with wild-type
heterozygote		were 1000-1250 mg/m <sup>2</sup> twice daily. Therapy was evaluated	patients.'
DPYD variant		after 1-2 cycles. Clinically relevant capecitabine-induced toxi-	
carriers: a single-		cities resulted in a dose reduction according to standard prac-	
center observatio-		tice, whereas no or minimal toxicities allowed for a 15% dose	
nal study.		escalation. In the remaining cases, the dose was maintained	
Anticancer Drugs		because of acceptable toxicities. The capecitabine dose could	
2019 Jan 8		be increased repeatedly on the basis of tolerability, but could	
[Epub ahead of		never exceed the conventional dose for the intended treat-	
print].		ment. As is standard practice, the patients' clinical condition	
PubMed PMID:		was also taken into account. Doses were only increased if the	
30628914.		patient had a good clinical condition and if oncologist and	
		patient agreed on increasing the dose.	
		The dose was increased in 6 patients and subsequently redu-	
		ced again in 2 patients. Of the 6 patients with a dose increase	
		1 (17%) experienced a grade 3 toxicity. 2 of the 11 patients	
		(18%) developed a grade 3 adverse event on the reduced	
		starting dose. For one patient with grade 3 diarrhoea the dose	
		was reduced because of this, for the other patient with grade 3	
		neutropenia, the dose was not reduced. The 3 patients main-	
		tained on the reduced starting dose because low-grade toxici-	
		ties and a moderate clinical condition did not allow for a dose	
		increase, developed disease progression. Of the 5 patients	
		who tolerated a dose increase, 2 developed disease progres-	
		sion and a 3 <sup>rd</sup> patient had his colon resected. A median dose	
		increase of 8.5% (range 4-31%) was achieved.	
		Diarrhoea and haematological toxicities grade $\geq$ 3 and hand-	
		foot syndrome grade $\geq$ 2 were considered severe.	
		Hospitalisations were defined as capecitabine treatment rela-	
		ted or possibly treatment related hospitalisations. Cycles were	
		noted only if at least 50% of the capecitabine days were com-	
		pleted.	
		Results were compared with 174 patients without gene variant	
		treated with normal dose capecitabine.	

	1	-			I	
ref. 1, continua- tion		Genotyping: - 7x gene activity score 1.5 (6x *1/1236A, 1x *1/2846T) - 4x gene activity score 1 (*1/*2A)				
		Results:				
		Result for carriers of a gen pared to non-carriers on th	e variant on reduced o e normal dose:	lose com-		
		outcome	value for			
				non-		
	AS 1 1 5		NO	carriers		
	on aeno-	toxicity	NO The % of natients	37.9%		
	type gui-	toxiony	with severe toxicity			
	ded dose:		was numerically			
	AA		lower for carriers of			
			reduced dose			
			(27.3%).			
		% of patients with diarrhoea grade ≥ 3	NS	19.5%		
		% of patients with	NS	11.5%		
		diarrnoea resulting in				
		% of patients with hand-	NS	20.1%		
		foot syndrome grade $\geq 2$				
		% of patients with	NS	3.4%		
		grade $\geq 3$				
		total prevalence of	NS	43.1%		
		severe toxicities	NIO			
		hospitalisations	NS	11.5% 8 days		
		lisation		0 days		
		cycle of first severe toxi-	NS	2		
		city				
		- Of the 6 patients with ger	notype *1/1236A:			
		- 2 tolerated a dose incre	ase in cycle 3 (to 83%	or 98% of		
		the normal dose). The	patient with the highes	t increa-		
		The other patient only r	noderately tolerated th	ycie 3. le dose		
		increase.	,			
		- 1 received an initial dos	e increase (to 85% of	the		
		the general condition cl	and 93% in cycle 3), b panging from good to r	ut due to		
		dose increase was reve	ersed (decrease to 85%	% of the		
		normal dose in cycle 4	and to 75% in cycle 6)	•		
		- 2 were maintained on the	ne starting dose, 1 due	e to a		
		of toxicity and 1 due to	arade 3 neutropenia ir	n cvcle 2		
		being accepted. The fire	st patient developed di	isease		
		progression (in cycle 2)	ation to 660/ is availy 0	offer		
		- Treceived a dose reduc	rred in cycle 1 In this	natient the		
		colon was resected.				
		- The mean dose in the las	st cycle was 78% of the	e normal	Tolerated dose	
		dose for these 6 patients	otvpe *1/28/6T tolerat	ed a dose	compared to AS 2:	
		increase in cycle 3 to 850	% of the normal dose.	She	AS 1.5: 79%	
		developed disease progr	ession in cycle 9.			
		- Of the 4 patients with ger	ne activity score 1 (*1/*	<sup>2</sup> 2A):		
		dose in cycle 2. 63% in	cycle 3 and 73% in cv	cle 4).		
	1	,,,	,	,		

ref 1 continua-		The natient received a colon resection in cycle 6	
tion		<ul> <li>1 developed grade 3 diarrhoea after dose increase to 59% of the normal dose in cycle 2.</li> <li>2 were maintained on the starting dose due to a mode-</li> </ul>	
		rate general condition (and either no or grade 1 toxi- city). Both developed disease progression (in respec-	
		- The mean dose in the last cycle was 54% of the normal dose for these 4 patients.	
		NOTE: Because 42% of patients were not genotyped for 1236G>A, approximately 4 patients in the group without gene variant, treated with the normal dose, were actually *1/1236A. However, reducing the number of patients experiencing toxicity in the group without a gene variant with 4, still results in a numerically higher percentage of patients in the group without gene variant experiencing toxicity than in the group with gene variant (36% versus 24%).	
		NOTE: All patients were genotyped for *2A and 2846A>T. 58% of patients was also genotyped for *13 and 1236G>A. *13 was not found in these patients.	
ref. 2 – CAP, mono/comb Lunenburg CATC et al. Diagnostic and therapeutic strate- gies for fluoropyri- midine treatment of patients carry- ing multiple DPYD variants. Genes (Basel) 2018;9:E585.	2	6 patients with multiple gene variants were identified either by additional retrospective genotyping after development of toxi- city grade $\geq$ 3 from capecitabine-containing therapy in the study of Deenen 2016 (n = 4) or prior to treatment in routine clinical care (n = 2). One of these patients (with *2A and 2846T) was already described in Lunenburg 2016, but was included because the data on DPD activity are new for these patient. A 7 <sup>th</sup> patient (1236A/2846T), already described in Henricks 2017, was not included in this summary. DPD enzy- me activity in peripheral blood mononuclear cells was deter- mined either retrospectively after the occurrence of toxicity grade $\geq$ 3 (n = 4) or during treatment (n = 2).	Authors' conclusion: 'In patients carrying multiple DPYD vari- ants, we recom- mend that a DPD phenotyping assay be carried out to determine a safe starting dose.'
PubMed PMID: 30487465.		Genotyping: - 6x 'fenotyping' (3x *2A/1236A or *1/*2A+1236A, 3x *2A/2846T or *1/*2A+2846T)	
	FENO: F FENO on 50% of the nor- mal dose: AA	<ul> <li>Results:</li> <li>The 6 patients had 1%, 9%, 16%, 38%, 60% or 72% of the normal DPD activity (9%, 16% and 38% for *2A/1236A or *1/*2A+1236A; 1%, 60% and 72% for *2A/2846T or *1/*2A+2846T).</li> <li>Of the 2 patients with a DPD activity higher than 50% of normal, the patient with 72% of the normal DPD activity was verified to be *1/*2A+2846T (gene variants on the same allele), but the patient with 60% of the normal DPD activity was verified to be *2A/2846T (gene variants on separate alleles).</li> <li>the 4 patients with the lowest DPD activity had developed toxicity grade ≥ 3 (1x grade 3, 2x grade 4, 1x grade 5) on the normal dose. Three of them were admitted to hospital for 7-14 days. The authors indicate that low DPD enzyme activities might be due to neutropenia, because DPD activity is measured in mononuclear cells.</li> <li>the 2 patients with the highest DPD activity tolerated 50% of the normal starting dose (toxicity grade 0 for the patient with 72% of the normal DPD activity (starting dose based on the detection of the *2A allele prior to treatment in Deenen 2016) and grade 1-2 for the patient with 60% of the normal DPD activity (starting dose based on the genotype and the previous tolerance for adjuvant therapy</li> </ul>	Tolerated dose compared to AS 2: FENO: 50% DPD activity compa- red to AS 2: FENO: 33% (66% if measured prior to toxicity)

ref. 2, continua-		with 5-fluorouracil 600 m	g/m <sup>2</sup> as described e	arlier in				
tion		Lunenburg 2016)). A dos						
		for these patients. The patients	alliative therapy for	the patient				
		with 60% of the normal D	)PD activity was dis	continued				
		due to the side effects.	,					
		NOTE: Genotyping was for	*2A, *13, 1236G>A	and 2846A>T.				
ref. 3 – CAP/FU,	3	40 patients with genotype *	1/*2A and treated w	ith an approxi-	Authors' conclusion:			
mono/comb		mately 50% reduced fluorog	vrimidine dose wer	e compared to	'Our study is the first			
Henricks LM et al.		patients without *2A and to	patients without *2A and to *1/*2A treated with full dose. To					
Effectiveness and		compare efficacy, 37 *1/*2A	patients treated wi	th reduced	*2A genotype-gui-			
safety of reduced-		dose were matched to patie	nts without *2A, *13	3, 1236A, and	ded dosing appears			
dose fluoropyrimi-		2846T, treated with full dose	e. Only 13 matched	pairs could be	to have no negative			
dine therapy in		evaluated for disease control	ol. To compare safe	ty, *1/*2A	effect on effective-			
patients carrying		patients treated with a reduc	ced dose were com	pared with	ness of fluoropyrimi-			
the DPYD*2A		1606 patients without *2A tr	eated with full dose	from Deenen	dine-based chemo-			
variant: a		2016 and with 86 historical	controls (*2A-carrie	rs treated with	therapy, while resul-			
matched pair		full dose; including the histo	rical controls in Dee	enen 2016).	ting in significantly			
analysis.		16 of the 40 *1/*2A patients	were from the stud	y of Deenen	improved patient			
Int J Cancer		2016. The mean dose durin	g the first cycle of th	nese patients	safety.'			
2018 Nov 28		was 52% of the normal dose	e and during the en	tire treatment				
[Epub ahead of		duration 53%. It was allowed	d to titrate the dose	upwards				
print].		during treatment after two c	ycles based on tole	rance, as deci-				
PubMed PMID:		ded by the treating physicial	n. In 11 patients, do	ses were titra-				
30485432.		ted upwards during treatme	nt, in 7 patients dos	es had to be				
		further reduced after the init	ial dose reduction c	of 50%.				
		Overall survival was defined	as the time betwee	en initiation of				
		treatment and death by any	cause. Progression	n-free survival				
		was defined as the time bet	ween initiation of the	eatment and				
		signs or death whichever a	ssion by either rauk	biogy of clinical				
		response was defined account	rding to RECIST 1	1 criteria				
		Disease control was defined	taing to RECIST T.	nse partial				
		response or stable disease	a as complete respo	nise, partial				
		When anticipating a 15% de	crease in overall su	irvival (from				
		45% in the group without *2	A to 30% in the *1/*	2A-group at				
		the end of the study, with a	hazard ratio of no *	2A versus				
		$^{1/2}$ A of 0.66), 154 pairs (1	92 events in total)	will be needed				
		to reach 80% power, with a	5% significance lev	el. With the				
		37 pairs of patients in this st	tudv. onlv a differen	ce of at least				
		33% is detectable with 80%	power.					
		Genotyping:						
		- 1606x gene activity score	2 (37 for efficacy ar	nalysis)				
		- 40x gene activity score 1 (	*1/*2A) (37 for effic	acy analysis)				
		Results:		, <u></u>				
		Result for *1/*2A on approx	ximately 50% of the	e normal dose				
		compared to patients with	Dut "2A on the norm					
		outcome		value for				
				patients				
		modion overall over the	NC	Without ZA				
				24 MONUNS				
		survival	би	TO MONTAS				
	AS 1 on	% of patients with con-	NS	48%				
	guided	overall toxicity grade > 3	NS	23%				
	dose: AA	hand-foot syndrome	NS	5%				
		grade 3	_					
		haematological toxicity	NS	10%				
		grade ≥ 3						
		gastrointestinal toxicity	NS	9%				

ref. 3. continua-		$arade \geq 3$					
tion		treatment interruptions	NS	19%			
		treatment discontinuation due to toxicity	NS	16%			
		treatment-related hospi- talisation	NS	11%			
		treatment-related death	NS	0%			
	genotype	Result for *1/*2A on appro compared to *2A-carriers of	ximately 50% of the on the normal dose:	e normal dose			
	guided	outcome		value for			
	versus			*2A-carriers			
	not-geno-			on the nor-			
	ded thera-	overall toxicity grade $> 3$	RR = 0.23 (95%	77%			
	py for AS 1: AA <sup>#</sup>		Cl: 0.12-0.45) (S)				
		haematological toxicity grade ≥ 3	x 0.18 (S)	56%			
		gastrointestinal toxicity grade ≥ 3	x 0.26 (S)	38%			
		treatment-related death	trend for a decrease (p = 0.096) (NS)	8%			
		NOTE: Constyning was for	*20 For the 37 pat	ients without			
		*2A included in the efficacy	analysis, the prese	nce of 1236A,			
ref. 4 – CAP/FU.	3	828 patients were treated w	ith chemoradiation	with a fluoro-	Authors' conclusion:		
mono		pyrimidine. 22 patients with	DPYD variant allele	es treated with	'DPYD variant allele		
Lunenburg CATC		a reduced fluoropyrimidine of	dose and 34 patien	ts with DPYD	carriers who recei-		
et al.		variant alleles treated with t	he normal dose we	re compared to	ved dose reductions		
Standard fluoro-		dose in addition a *1/*2A c	alleles treated with	i the normal	(n = 22) snowed a		
ges in chemora-		wed by a strong dose increa	ase was described.	Starting doses	quency of severe		
diation therapy		in 22 patients with DPYD va	ariant alleles were re	educed to 50%	gastrointestinal toxi-		
result in an		or 75 <sup>'</sup> % of the normal startin	g dose according to	o Dutch Phar-	city compared with		
increased risk of		macogenetics Working Grou	up 2015 and Clinica	al Pharmacoge-	wild-type patients,		
Severe toxicity in		netics Implementation Cons	sortium 2017 guidel	Ines (I.e. 50%	but more (not statis-		
allele carriers		for $*1/1236A$ 495 of the 82	A, 00% 101 1/2040 8 natients were froi	n the study of	severe haematolo-		
Eur J Cancer		Deenen 2016. In addition, 2	40 patients from the	e Leiden Uni-	gical toxicity. Hospi-		
2018;104:210-8.		versity Medical Center and	93 from the Italian (	Cancer Insti-	talisations for all		
PubMed PMID:		tute were included in the an	alysis. Differences	in toxicities	DPYD variant allele		
30361102.		were observed between the	is different (for eval	oradiotherapy	carriers were com-		
		bine 825 mg/m <sup>2</sup> twice daily	dent of dose adjust-				
		$mg/m^2$ twice daily for 2 wee	$na/m^2$ twice daily continuously instead of 1250 $na/m^2$ twice daily for 2 weeks followed by 1 week rest for				
		(colo)rectal cancer).	-		mean duration of		
		Of the gastrointestinal toxici	ity, diarrhoea and m	nucositis were	hospitalisation was		
		scored for all of the included	d patients, but naus	ea and vomi-	significantly shorter		
		Leiden group respectively.	Leiden plus Italian	groups and the	tion group.'		
		Genotyping:					
		Reaucea aose group:		ןוֹסטעם: ∽t 2 (*1/*1)			
		- 12x gene act. 1.5 (11x	- 20x dene act	. 1.5 (20x			
		*1/1236A, 1x *1/2846T)	*1/1236A, 9x	(*1/2846T)			
		- 10x gene act. 1 (*1/*2A)	- 3x gene act.	1 (2x *1/*2A,			
			1x *1/*13) 2x 'fana' (40)	061/10261			
			- 2x ieno (123	DUA/1230A)			

rof 1 continue		Populto:	<u> </u>			
ref. 4, continua-		Results:				
		Result for gene variant car	riers on reduced ad	ose compared		
		to gene activity 2 on the no	ormai dose:			
		outcome		value for		
				gene act. 2		
				on normal		
				dose		
		overall toxicity grade $\geq 3$	NS	13.6%		
		haematological toxicity	trend for an	2.9%		
		grade ≥ 3	increase (p =			
	AS 1-1.5		0.083) (NS)			
	on geno-	gastrointestinal toxicity	NS	8.0%		
	type qui-	grade ≥ 3				
	ded dose:	dose reductions	NS	4.4%		
	AA	dose increases	NS	0.5%		
		treatment interruptions	NS	4.9%		
		prematurely stopped	NS	9.9%		
		treatment-related hospi-	NS	7.8%		
		talisation				
		days of hospitalisation	NS	13		
		days of hospitalisation		10		
		Result for gene variant car	riers on normal dos	e compared		
		to gene activity 2 on norm		se compared		
				value for		
		outcome				
				gene act. Z		
				on normal		
			NO	dose		
		overall toxicity grade ≥ 3	NS 1.10	13.6%		
		haematological toxicity	$OR_{adj} = 4.19$	2.9%		
	19115	grade ≥ 3	(95% CI: 1.32-			
	45 1-1.5 + EENIO:		13.25) (S)			
		gastrointestinal toxicity	OR <sub>adj</sub> = 2.58	8.0%		
	L	grade ≥ 3	(95% CI: 1.02-			
			6.53) (S)			
		dose reductions	NS	4.4%		
			Doses were			
			reduced from			
			100 to 60-77%.			
		dose increases	NS	0.5%		
		treatment interruptions	NS	4.9%		
		prematurely stopped	NS	9.9%		
		treatment-related hospi-	NS	7.8%		
		talisation				
		days of hospitalisation	NS	13		
		· ·	•			
		Result for gene variant car	riers on reduced do	se compared		
	genotype	to gene variant carriers on	the normal dose:	'		
	genotype	outcome		value for		
	yulueu			carriers on		
	versus			normal		
	tuno qui			dose		
	type gui-	treatment-related bosni-	NS	17.6%		
	ueu inera-	talisation		17.070		
	1 1 5, A A#	days of bospitalisation	x 0 17 (S)	23		
	1-1.5. AA"		x 0.11 (0)	20		
		<ul> <li>One *1/*2A was started of Despite diarrhoea grade increased to 83% of the r severe toxicity (diarrhoea dermatitis grade II) occur later radiotherapy, was s was hospitalised for 31 d</li> </ul>	on 50% of the norm I-II after 2 weeks, the normal dose. After a, vomiting, nausea red, and chemothe topped prematurely of which 3 d at the	al dose. ne dose was 4 weeks, grade III and rapy, and 7. The patient e intensive		
			, or written o'u at the			

ref. 4, continua-	care unit. After ho	ospitalisation, the patient had t	o recover	
tion	bilitation).	oxicity for 39 d in a nursing no	ome (rena-	
	· · · · · · · · ·			
rof 5 - CAP/FU 3	NOTE: Genotyping v	was for *2A, *13, 1236G>A an ither no or a single gene varia	<u>d 2846A&gt;T.</u> nt were	Authors' conclusion:
mono/comb	treated with genotyp	be-guided fluoropyrimidine-bas	sed chemo-	'Prospective DPYD
Henricks LM et al.	therapy for a mediar	n of 71 days. The median num	ber of treat-	genotyping was
DPYD genotype-	ment cycles was 3. I	Patient without a gene variant	received the	feasible in routine
guided dose indi-	normal starting dose	2. "1/"2A and "1/"13 received to *1/1236A and *1/2846T received to the second seco	ou% of the	DPYD genotype-
fluoropyrimidine	the normal starting dose	lose. Dose increase was allow	ved after the	based dose reduc-
therapy in pa-	first two cycles provi	ided that treatment was well to	olerated, and	tions improved pa-
tients with cancer:	the decision was left	t to the discretion of the treatin	g physician.	tient safety of fluoro-
a prospective AS 1.3	: F For one ^1/^28461 n	to dose reduction was applied	. The patient	pyrimidine treat-
Lancet Oncol	than 4 times as ofter	n in patients with a gene varia	nt (13% of	and c.1679T>G car-
2018;19:1459-67.	patients) than in pati	ients without a gene variant (3	% of pa-	riers, a 50% initial
PubMed PMID:	tients). The dose inc	crease was not well tolerated i	n 6 of the 11	dose reduction was
30348537	patients with a gene	variant (2 of the 4 *1/*2A, 3 o	f the 4	adequate. For
and personal	in the *1/2846T disc	ontinuing therapy because of	toxicity and	c 2846A>T carriers
communication	a dose reduction in t	the other patients. So, in 8% c	of the 85	a larger dose reduc-
(titrated dose and	patients with a gene	variant, intolerance/toxicity w	as caused	tion of 50% (instead
median DPD	by either a dose incr	rease or the starting dose not	being redu-	of 25%) requires
activity)	Toxicities scored as	possibly probably or definite	ly related to	investigation.
	fluoropyrimidine trea	atment were considered treatm	nent-related.	
	DPD enzyme activity	y in peripheral blood mononuc	lear cells	
	was determined in p	pre-treatment samples (in 56 p	atients with	
	Relative toxicity risks	s for patients without).	ant and	
	patients without a ge	ene variant were compared to	the relative	
	risks in a historical c	control of patients receiving no	t-genotype-	
	guided therapy (i.e. t	the normal starting dose for al	l patients)	
	Sample size calculat	tions revealed a required sam	ple size of	
	11 variant carriers.	·	•	
	Construing			
	- 1018x gene activity	v score 2 (*1/*1)		
	- 68x gene activity s	core 1.5 (51x *1/1236A, 17x *	1/2846T)	
	- 17x gene activity se	core 1 (16x *1/*2A, 1x *1/*13)	,	
	Results:			
	Result for gene var	riant carriers on reduced dose	compared	
	to patients without	gene variant on the normal do	se:	
AS 1	on		value for	
75% c			without	
the no	-		gene	
mal st	ar-		variant	
		arriers x 1.7 (5)	23%	
	toxicity	230A   KK = 1.69 (95% CI: 1.18-2.42) (S)		
AS 1 0	n *1/28	346T RR = 2.00 (95% CI:	1	
the nc	-	1.19-3.34) (S)		
mal st	ar-	A NS	4	
ting de	se:   arade ≥ 3 gastroint	estinal x 2 5 (S)	8%	
AA	toxicity		0,0	
	grade ≥ 3 haemato toxicity	logical x 2.5 (S)	6%	

rof 5 continua	grade 2 hand for	n NG 40/				
tion	grade 3 hand-loc	ot syn-	NS		4%	
tion	arome			101		
	grade $\geq 3$ cardiad	c toxicity	NS		1%	
	grade ≥ 3 other t	reat-	NS		8%	
	ment-related toxi	city				
	overall grade ≥ 4	NS		3%		
	grade ≥ 4 gastroi	ntestinal	NS		1%	
	toxicity					
	arado > 4 baoma	tological	NS		10/	
	tovicity	llological	IN S		1 70	
	grade ≥ 4 cardiad	c toxicity	NS		<1%	
	grade ≥ 4 other t	reat-	NS		1%	
	ment-related toxi	city				
	fluoropyrimidine-	related	NS		14%	
	hospital admissio	on				
	stop of fluoropyri	midines	NS		17%	
	because of adver	rse			11 /0	
	events	30				
	fluerenvrimidine	rolotod	NC		<10/	
	fluoropyrimiaine-	related	NS		<1%	
	death					
	Results per varia	nt genoty	pe:			
	•	*1/	*1/	*1/*2A	*1/*13	
		1236A	2846T	.,	.,	
	% of normal	7/	73	51	50	
	dooo in first	/ 4	15	51	50	
	cycle					
	% of normal	74	72	53	54	Titrated dose com-
	dose whole					pared to AS 2:
	treatment					AS 1.5: 72%
	titrated dose	74	64	57	63	AS 1: 57%
	DPD-enzyme	80	66	55	40	
	activity (% of					DPD activity compa-
	normal)					red to AS 2
	median DPD-	74	67	56		AS 1 5: 77%
	enzyme activity	17	07	50	_	AS 1: 53%
	(% of pormal)					AG 1. 55%
					_	
	Relative risk (959	% CI) for c	overall grad	$le \ge 3$ toxicit	y for car-	
	riers on reduced	dose com	pared to c	arriers on the normal		
	dose:					
	red	uced dose	е	normal do	se	
	1236G>A 1.6	9 (1.18-2.	42) (S)	1.72 (1.22	-2.42) (S)	
	2846A>T 2.0	0(119-3)	$\frac{7}{34}$ (S)	3 11 (2 25	-4.28) (S)	
	*20 10/11 2.0	1 (0.63.2	73) (NS)	2 87 (2.20	3.86) (S)	
	*10	1 (0.00-2.	73)(10)	2.07 (2.14	-3.00(0)	
	13   -			4.30 (2.10	-0.00) (3)	
	NOTE: The author	rs did not	investigate	whether the	e overall	
	grade ≥ 3 toxicity i	n carriers	on reduce	d dose after	correction	
	for the toxicity cau	sed by do	se increas	e and exclu	sion of the	
	patient that never	received a	a dose redi	uction was s	still sianifi-	
	cantly higher than	in patient	s without a	ene variant	on full dose	
	This correction rec	luces the	overall ara	de > 3 toxic	ity in all	
	carriers from 20%	to 21% in	- *1/1226A	from 20% t	a 22% and	
	in *1/2046T frame	10.5170, 11	1 1/1230A	*0 A this so	0 33 /0 anu	
		F7 % 10 30	70. (FUI I/			
	reduces the overa	ii grade ≥		rom $31\%$ to	19%, while	
	the value for *1/*1	3 remains	s U%.)			
	NOTE: The author	rs indicate	ed that altho	ough the me	ean DPD	
	enzyme activity fo	r *1/1236/	A was redu	ced by arou	nd 20%, the	
	large variation in t	his activitv	/ suggests	that a propo	ortion of	
	patients needs a la	arger dose	e reduction	, while othe	r patients	
		<u> </u>			-	

ref. 5, continua- tion		might tolerate a tion between DI severe fluoropy pes, also for *1/ important role of toxicity. NOTE: In the di applied genotyp underdosing/un this issue in the dose reduction close monitoring titrated dose in the normal dose remaining mean starting dose of these patients.	full dose. Howeve PD enzyme activit rimidine-related to /236A (and for *1/2 of DPD activity vari- iscussion, the auth be-guided dose re- idertreatment. How ir recommendation of 50% for *1/236, g and individual do these patients is r e and correspondin n and median DPD 50% would be un	er, the absence of y and the occurre oxicity for each of 2846T), argues a iation in the occu nors mentioned to duction is unlikely vever, they did no n of a more cauti A and *1/2846T, ose titration. Beca espectively 74% ng percentages fo activity were for derdosing for the	of a correla- ence of the genoty- gainst an rrence of wice that the y to result in ot address ous initial followed by ause the and 64% of or the und, a e majority of	
ref. 6 – CAP/FU, comb Madi A et al. Pharmacogenetic analyses of 2183 patients with advanced colo- rectal cancer; potential role for common dihydro- pyrimidine dehy- drogenase vari- ants in toxicity to chemotherapy. Eur J Cancer 2018;102:31-9. PubMed PMID: 30114658.	3	NOTE: Genotyp 2116 patients w with fluoropyrim cetuximab for 2 bine plus oxalip plus oxaliplatin. After 12 weeks, ous or intermitte Any 12-week to in chemotherap toxicity except p is an oxaliplatin Associations we zygous variant y type). Odds rati fitted the data (a ant versus hom gous variant ve additive (i.e. ho homozygous wi and type of fluo The power was with frequencies variants with fre vely a 7% differ and 35% had to Genotyping: 2846A>T (Asp - 2086x *1/*1 - 30x *1/2846T Results: Results for gel without the ge	bing was for *2A, * vith advanced color hidine-oxaliplatin c 4 weeks. 62% of p latin and 38% rec 37% of patients a therapies also dif- ent. which was defined by in the first 12 we beripheral neuropa- associated toxicit are tested with a c versus heterozygous mozygous wild type rsus heterozygous mozygous variant ild type)) and were ropyrimidine. > 85% to detect c s > 20% and to de equencies > 5%. T ence in response bxicity) and an 11% b949Val): f ne variant carriers ne variant carriers ne variant: 2846A>T	13, 1236G>A an         rectal cancer we         hemotherapy wit         batients received         eived infusional 5         also received cetu         fered in being eit         as a dose reduc         batients received cetu         fered in being eit         as a dose reduc         bats of treatment         athy. Peripheral m         y.         odominant mode         bus versus homoz         d using the best m         hozygous+heteroo         y. recessive (i.e.         s+homozygous w         versus heterozyge         adjusted for cet         bdds ratios of 1.3         tect odds ratios of 1.3         tect odds ratios of 1.45% r         6 difference in re         2A (2105 patient         bed):         2082x *1/*1         23x *1/*2A         compared to patient         *2A         NS	d 2846A>T. re treated h or without capecita- 5-fluorouracil uximab. ther continu- tion or delay due to any neuropathy el (i.e. homo- zygous wild model that zygous vari- homozy- rild type), or gous versus uximab use for variants of 1.6 for to respecti- responded sponse. s genoty- tients value for pa- tients value gene variant 36%	Authors' conclusion: 'Our data suggest that both common and rare DPYD vari- ants may be asso- ciated with toxicity to fluoropyrimidine- based chemothera- py No common variant associations remained significant after Bonferroni cor- rection.'
		tion or the-	CI: 1.1-4.5)			

rof C continue			(O hut NO offer			
ref. 6, continua- tion		rapy delay in the first 12 weeks due to any toxicity ex- cept peri- pheral neu- ropathy neutropenia	(S, but NS after correction for the 8 tested gene variants) OR = 3.2 (95%	NS	13%	
		grade ≥ 2	CI: 1.2-8.2) (S, but NS after correction for the 8 tested gene variants)			
		lethargy grade ≥ 2	NS	OR = 5.3 (95% CI: 1.9-14.9) (S, also after correction for the 8 tested gene variants)	34%	
		nausea and vomiting grade ≥ 2	OR = 3.4 (95% CI: 1.5-7.3) (S, also after correction for the 8 tested gene variants)	NS	20%	
	AS 1.5: D	diarrhoea grade ≥ 2	OR = 4.6 (95% Cl: 2.1-10.1) (S, also after correction for the 8 tested gene variants)	OR = 4.4 (95% Cl: 1.7-11.0) (S, also after correction for the 8 tested gene variants)	25%	
		stomatitis grade ≥ 2	NS	OR = 4.6 (95% CI: 1.7-12.6) (S, also after correction for the 8 tested gene variants)	10%	
		hand-foot syndrome grade ≥ 2	NS	OR = 3.8 (95% CI: 1.2-11.8) (S, but NS after correction for the 8 tested gene variants)	9%	
	AS 1: E	infection with neutro- penia grade ≥ 3	OR = 5.5 (95% CI: 1.3-24.2) (S, but NS after correction for the 8 tested gene variants)	OR = 19 (95% CI: 5.0-73.8) (S, also after correction for the 8 tested gene variants)	3%	
		NOTE: Only da ted with toxicity ded in the table For the commo (Val732IIe), this and an increase vely. However, correction for m specific toxicitie ciation with neu- red after correct encoding gene	ata on the gene var x and reduced DPE x above. on gene variants *9 s study found an as e in any toxicity in significance disap nultiple testing. For es were found. For utropenia grade $\geq 2$ ction for the testing.	iants proven to be enzyme activity w A (Cys29Arg) and ssociation with a de the first 12 weeks i peared after Bonfe *9A, no associatio *6, this study foun 2, but significance of of 8 variants of the	associa- /ere inclu- *6 ecrease erespecti- erroni ons with d an asso- disappea- e DPD	

rof 6 continua-		The study found an association of $*4$ (Ser534Asn) with any	
tion		toxicity in the first 12 weeks, but not with specific toxicities and	
uon		conclusion of a set of the servention for the testing of a veri	
		significance was lost after correction for the testing of 6 vari-	
		The study found on second stars of 775 Ab O (Luc 050 Oly) with	
		The study found an association of 775A>G (Lys259Giu) with	
		stomatitis, but significance was both lost after calculation of an	
		odds ratio and after correction for the testing of 8 variants of	
		the DPD encoding gene.	
		The study found no association of 496A>G (Met166Val) and	
		1627A>G (Ile543Val) with either any or specific toxicity.	
		So, the study confirms the lack of sufficient proof for an asso-	
		ciation with toxicity for these gene variants.	
		NOTE: Genotyping was for the indicated gene variants.	
ref. 7 – CAP,	2	A 59-year-old women with 0.5% of the normal DPD activity	Authors' conclusion:
comb		tolerated adjuvant chemotherapy with 0.8% of the normal	'This case report
Henricks LM et al.		capecitabine dose (77 mg/m <sup>2</sup> on days 1 and 6 of the first cycle	demonstrates that a
Capecitabine-		and on days 1, 6 and 11 of the following cycles) in combina-	more comprehen-
based treatment		tion with oxaliplatin for eight cycles. Capecitabine-related toxi-	sive genotyping and
of a patient with a		city like diarrhoea, hand-foot syndrome or leukopenia did not	phenotyping ap-
novel DPYD		occur. However, sensory neuropathy developed during the	proach combined
denotype and		first cycle, and became more severe (grade 3) during the	with pharmacokine-
complete dihydro-		second cycle. Because this was most likely caused by ovali-	tically-quided dose
pyrimidine deby-		platin, the ovalinlatin dose was decreased to 75% from the	administration ena-
drogenase defi		third cycle onwards and discontinued after the sixth cycle	bles save fluoropy
ciency	AS 0: A	The dose corrected AUC of fluorouracil in this patient was	rimiding treatment
Int I Cancor	AS 0. A	11 271% of that of control nationts	with adequate drug
		11.271% of that of control patients.	
2010,142.424-30.		Her genotype was ZA/(duplication of exon 17 and 16).	tak DDD deficient
		NOTE: The metions was initially menetimed for \$0.0, \$40, 00.40	tery DPD delicient
28929491.		NOTE: The patient was initially genotyped for "2A, "13, 2846	patients.
		A>1 and 1236G>A. Additional gene variants were not found	Description
		by sequencing of all 23 coding exons and flanking intronic	Dose-corrected
		regions, after which copy numbers of sequences were analy-	AUC versus AS 2:
		sed	AC 0. 110710/
	-		AS 0. 1127170
ref. $8 - CAP/FU$ ,	2	5 patients, being either homozygous for a gene variant or	Authors' conclusion:
mono/comb	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-	Authors' conclusion: 'We showed that
mono/comb Henricks LM et al.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment	Authors' conclusion: 'We showed that fluoropyrimidine
<b>mono/comb</b> Henricks LM et al. Treatment algo-	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat-	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo-	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno-	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com-	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy-	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari-	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi-	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> .	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> .	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping:	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping: - 2x 1236A/1236A	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping: - 2x 1236A/1236A - 2x 2846T/2846T	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs,
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping: - 2x 1236A/1236A - 2x 2846T/2846T - 1x *2A/*2A	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping: - 2x 1236A/1236A - 2x 2846T/2846T - 1x *2A/*2A - 1 carrier of both 1236A and 2846T (verified as 1236A/2846T	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: - 2x 1236A/1236A - 2x 2846T/2846T - 1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat-
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ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5- fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treat- ment DPD activity was also determined in a patient with geno- type 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determi- ned, normalised to a dose of 850 mg/m <sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m <sup>2</sup> . Genotyping: - 2x 1236A/1236A - 2x 2846T/2846T - 1x *2A/*2A - 1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018) Results:	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole-
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ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul> </li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had</li> </ul> </li> </ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 EENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> </ul> </li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity</li> </ul> </li> </ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul> </li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine</li> </ul></li></ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul> </li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine dose in cycle 1 and with 100% in cycle 2. The second</li> </ul></li></ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi- vidually titrated
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> </ul> </li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine dose in cycle 1 and with 100% in cycle 2. The second was treated with 50% of the normal 5-fluorouracil dose</li> </ul> </li> </ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi- vidually titrated according to tole-
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul> </li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine dose in cycle 1 and with 100% in cycle 2. The second was treated with 50% of the normal 5-fluorouracid dose. The natients did not have severe toxicity on the reduced</li> </ul></li></ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi- vidually titrated according to tole- rance '
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> </ul> </li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine dose. The patients did not have severe toxicity on the reduced doses</li> </ul> </li> </ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi- vidually titrated according to tole- rance.'
ref. 8 – CAP/FU, mono/comb Henricks LM et al. Treatment algo- rithm for homo- zygous or com- pound heterozy- gous DPYD vari- ant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.	2 FENO: A	<ul> <li>5 patients, being either homozygous for a gene variant or having two different gene variants, received capecitabine or 5-fluorouracil treatment with doses based on the pre-treatment DPD activity in peripheral blood mononuclear cells. Pre-treatment DPD activity was also determined in a patient with genotype 2846T/2846T, who did not receive treatment, because she was disease free after surgery. For 3 patients, the AUC of fluorouracil after the first dose of capecitabine was determined, normalised to a dose of 850 mg/m<sup>2</sup> and compared to 22 patients from another study receiving combined chemotherapy with capecitabine 850 mg/m<sup>2</sup>.</li> <li>Genotyping: <ul> <li>2x 1236A/1236A</li> <li>2x 2846T/2846T</li> <li>1x *2A/*2A</li> <li>1 carrier of both 1236A and 2846T (verified as 1236A/2846T (variants on separate alleles) by Lunenburg, Genes 2018)</li> </ul> </li> <li>Results: <ul> <li>Of the four patients homozygous for a partially functional allele, the two patients with genotype 1236A/1236A had respectively 79% and 42% of the normal DPD activity. The first was treated with 75% of the normal capecitabine dose. The patients did not have severe toxicity on the reduced doses. The patients with genotype 2846T/2846T had</li> </ul></li></ul>	Authors' conclusion: 'We showed that fluoropyrimidine treatment in homo- zygous or com- pound heterozygous DPYD variant allele carriers is feasible and that therapy does not have to be withheld. Additional DPD phenotyping tests, such as mea- surement of DPD activity in PBMCs, are recommended to compose an indi- vidualized treat- ment. After an initial dose reduction, tole- rability in patients should be monitored closely, and the dose should be indi- vidually titrated according to tole- rance.'

ref. 8. continua-		respect	ively 29% and 10% of the n	ormal DPD activity		
tion		The firs	t was treated with 17% of th	ne normal capecitabine		
		dose (2	78 mg/m <sup>2</sup> once daily in con	bination with radiothe-		
		rapy as	neoadjuvant treatment) an	d the second was the		
		patient	who did not need treatment	. The first patient tole-		
		rated tre	eatment well without occurr	ence of severe toxicity		
		and sur	gery was performed after tr	eatment. The dose-		
		correcte	ed AUC of 5-fluorouracil in t	his patient was 866%		
		of that of	of control patients.			
		The me	an DPD activity in these pa	tients was 40%. There		
		was a la	arge variance in DPD activit	ty between these		
		patients	<u>s (10-79%).</u>			
		- The pat	ient with genotype ^2A/^2A	had undetectable DPD		
		activity	and tolerated monotherapy	with 0.65% of the $r^2$ events 5 deve) for 1	Dose corrected	
		month	after which grade 2 diarrhoe	a developed After a	AUC versus AS 2	
		rest per	iod of 3 weeks treatment w	a developed. Aller a	FENO: 546%	
		same d	ose but every third dift was	skinned (0.43% of the	AS 0: 13812%	
		normal	dose). The patient tolerated	this dose also after		
		addition	of oxaliplatin and bevacizu	imab as originally		
		planned	and had stable metastatic	colorectal carcinoma	Tolerated dose	
		as best	treatment response.		compared to AS 2:	
	AS 0: A	The dos	se-corrected AUC of 5-fluor	ouracil in this patient	FENO: 55%	
		was 13.	812% of that of control pati	ents.	AS 0: 0.43%	
		- The car	rier of both 1236A and 284	6T had 45% of the		
		normal	DPD activity, corresponding	g to a patient with		
		variants	s on different alleles. He wa	s treated with 51% of	DPD activity compa-	
		the nor	nal capecitable dose in cy	cle 1 (dally dose of	EENO: 41%	
		900 mg	d without toxicity Increase	to 71% of the planned	AS 0. 0%	
		dose (d	ally dose of $1250 \text{ mg/m}^2$ in	cycle 2 resulted in		
		grade 3	thrombocytopenia. The do	se was reduced to		
		57% of	the normal dose (1000 mg/	m <sup>2</sup> daily), which was		
		continu	ed during cycle 3. However	, because grade 2		
		thrombo	ocytopenia developed after	8 days, the dose was		
		reduced	d to 29% of the normal dose	e (500 mg/m <sup>2</sup> daily) for		
		the rest	of the cycle, resulting in pla	atelets to increase to		
		normal	values. Progression of met	astatic colorectal		
		cancer	was established after 3 cyc	les and capecitabine		
		The dec	ant was discontinued.	ourooil in this nationt		
	FENO: A	Was 22	7% of that of control nation			
		Wa3 22		5.		
		NOTE: Pa	tients were genotyped for *	2A. *13. 2846A>T and		
		1236G>A.	5 71			
ref. 9 – FU,	4	1606 *2A-i	negative patients from Deer	nen 2016 were genoty-	Authors' conclusion:	
mono/comb		ped for oth	er gene variants.		'None of the indivi-	
Meulendijks D et		Toxicity wa	as defined as toxicity grade	≥ 3, global toxicity as	dual DPYD variants	
al.		any toxicity	y, hospitalisation as toxicity	related hospitalisation.	were found to be	
Pretreatment		Only outco	omes during the first cycle c	f chemotherapy were	associated with	
serum uracil		Included.	adjusted for any say and t	rootmont rogimon	global severe toxici-	
a predictor of		OKS were	adjusted for age, sex and t	reatment regimen.	and c 1670T>G	
severe and fatal		Genotypin	a.		combined there	
fluoropyrimidine-		- 19 carrie	s of 2846T		was evidence for an	
associated toxi-		- 3 carriers	s of *13		association with	
city.		- 58 carrie	rs of 1236A		global severe toxi-	
Br J Cancer					city. In addition,	
2017;116:1415-		Results:	Results:			
24.		Result fo	r carriers compared to non-	carriers of the gene	alone was associa-	
PubMed PMID:		variant:			ted with haematolo-	
28421081.		gene	outcome	UR <sub>adj</sub> (95% CI)	gical toxicity.	
		variant				

ref. 9, continua-		2846T	global toxicity	NS, trend for an in-	
tion				crease (p = 0.095)	
			gastrointestinal toxicity	NS	
			haematological toxicity	NS, trend for an in-	
				crease (p = 0.066)	
		*10	hospitalisation	NS	
		*13	global toxicity	NS	
			gastrointestinal toxicity	NS, trend for an in-	
			he exected a vised to visit (	crease ( $p = 0.090$ )	
	AS 1: E			24.9 (1.74-354) (S)	
			nospitalisation	$r_{rease}$ ( $p = 0.094$ )	
	AS 1 1 5.	2846T	dobal toxicity	30(105-877)(S)	
	F	and *13	giobal toxicity	0.0 (1.00-0.77) (0)	
		1236A	global toxicity	NS	
	AS 1.5:	1200/1	gastrointestinal toxicity	NS	
	AA		haematological toxicity	NS	
			hospitalisation	NS. trend for an in-	
				crease ( $p = 0.069$ )	
		For the 3	gene variants combined, s	ensitivity was 6%.	
		specificit	y 95%, positive predictive v	alue 13% and negative	
		predictive	e value 88% for prediction of	of global toxicity grade	
		$\ge 3$ in the	e first cycle.	5 , 5	
		NOTE: No	association was found for	the gene variants *4 (84	
		carriers), e	except for a trend for gastro	intestinal toxicity.	
		However,	most studies including a me	eta-analysis (Meulendijks	
		2015) do r	not show an association of t	his gene variant with	
		toxicity. In	addition, results regarding	the effect on DPD acti-	
		vity are inc	consistent.		
ref. 10 - FU/CAP,	2	A 51-year	old male developed severe	colitis with mucous	Authors' conclusion:
mono/comb		stools (gra	de 4 toxicity) and neutrope	nic fever (neutrophils	'The utility of phar-
Kodali S et al.		0.18x10 <sup>9</sup> /L	<ul> <li>) on day 21 of neoadjuvant</li> </ul>	t treatment with standard	macokinetic-based
Capecitabine-		dose cape	citabine (825 mg/m <sup>2</sup> twice o	daily) and radiotherapy.	dosing remains
induced severe	AS 1: E	His genoty	/pe was *1/*2A.		questionable as pa-
toxicity secondary		The patier	nt tolerated adjuvant therap	y with 5-fluorouracil 300	tients experienced
to DPD deficiency		mg/m² per	day as a continuous intrav	enous infusion (25% of	toxicity even with
and successiul		the standa	and dose) and without bolus	Injections of 5-huoro-	50% dose reduction
doco 5 fluorouro		thow woro	iudged net to influence rea	urropco or survival	monded by current
cil		uley were	Judged not to initidence reco		
J Gastrointest					lines. We therefore
Cancer					suggest that dosing
2017:48:66-69					of 5-FU should be
PubMed PMID:					customized in pa-
26744322.					tients with DPD defi-
					ciency based on cli-
					nical judgment ta-
					king into account the
					severity of toxicity
					from initial expo-
					sure.'
ref. 11 – CAP,	2	Three pati	ents treated with capecitab	ine containing chemo-	Authors' conclusion:
mono/comb		therapy w	ere retrospectively determin	ned to have genotype	'The presented func-
Meulendijks D et		1236A/123	36A. Gene variants *2A, *13	3 and 2846T were not	tional and clinical
al.		present in	tnese patients. More than 4	weeks after the last	data indicate that
Patients homozy-		treatment	with fluoropyrimidines, DPL	enzyme activity in	the c.1129-5923
gous for DPYD			blood mononuclear cells w	as determined and	U>G variant is both
0.1129-09230>G/		CDINA Was	analyseu.		dinically relevant
		Popultor			onnicany relevant,
deficiency and		$\Delta 47$ voc	r old female developed lau	kocytonenia grado 2	unfront dose roduc
		(2 2v109	ii olu lemale uevelopeu leul (L) neutropenia grada 2 (1	$3 \times 10^{9}$ /L) hand foot	tion of the fluoropyri
require a uuse		(2.3710)	$\mathbf{L}_{j}$ , neutropenia grade Z (1.	0x10/L), hanu-100l	

reduction when treated with fluo- ropyrimidines. Cancer Chemo- ther Pharmacol 2016;78:875-80. PubMed PMID: 27544765. ref. 11, continua- tion		syndrome grade 1, diarrhoea grade 1 and fatigue grade 1 on day 9 of neoadjuvant treatment with standard dose capecita- bine (825 mg/m <sup>2</sup> twice daily) and radiotherapy. Because the symptoms intensified, the capecitabine dose was reduced by 40% on day 15. After dose reduction, treatment was well tolerated. Five days after a dose increase by 10%, she again developed leukopenia grade 2 (2.5x10 <sup>9</sup> /L) and neutropenia grade 1 (1.5x10 <sup>9</sup> /L). Despite this, treatment could be finished at reduced dose. The patient received surgery and was disease-free four years after treatment. The DPD activity of the patient was 41% of the normal DPD activity.	midine starting dose in patients carrying c.1129-5923C>G homozygously.' Tolerated dose ver- sus AS 2: FENO: 60%
	FENO: C	<ul> <li>A 67-year old male developed fatigue grade 2 on day 7 of treatment with capecitabine 850 mg/m<sup>2</sup> on day 1-14 of the three-week cycle, docetaxel, oxaliplatin and bevacizumab. On day 11, the patient was hospitalised with neutropenia grade 2 (1.3x10<sup>9</sup>/L) and fever grade 1 (38.7°C, without apparent focus). After release from hospital, he refused further treatment.</li> <li>Because of disease progression, capecitabine 800 mg/m2 twice daily (64% of the standard dose) was started four months later as monotherapy. The patient again developed fatigue grade 2 and refused further treatment after cycle 1. The DPD activity of the patient was 55% of the normal DPD activity.</li> <li>A 69-year old male tolerated 4 weeks of neoadjuvant treatment with standard dose capecitabine (825 mg/m<sup>2</sup> twice daily) and radiotherapy well. Treatment was completed without dose reductions or delays, and without adverse events and haematological changes. The patient had a relapse one year after surgery and died as a result of progressive disease before determination of DPD activity could be performed.</li> <li>cDNA analysis of the first two patients showed that they produced roughly equal amounts of wild type mRNA and aberrantly spliced mRNA with a premature stopcodon.</li> <li>The authors indicate that the starting dose of capecitabine was relatively low in these patients (compared to the monotherapy dose of 1250 mg/m<sup>2</sup> twice daily). So, higher doses might have resulted in more pronounced toxicity. Amstutz 2009 describes a patient with genotype 1236A/1236A, who developed fatal toxicity during the first cycle with full-dose 5-FU plus cisplatin.</li> <li>NOTE: Patients were genotyped for 1129-5923C&gt;G and checked for the presence of 1236G&gt;A and 959-51T&gt;G, which are in complete linkage disequilibrium with 1129-5923C&gt;G in haplotype B3.</li> </ul>	DPD activity versus AS 2: FENO: 48%
ref. 12 – FU/CAP, mono/comb Lunenburg CA et al. Evaluation of clini- cal implementa- tion of prospective DPYD genotyping in 5-fluorouracil- or capecitabine- treated patients. Pharmacogeno- mics 2016;17:721-9.	3	The results of routine prospective genotyping and genotype- guided dosing were retrospectively evaluated in patients receiving capacetabine or 5-fluorouracil, either as combined chemotherapy (different combinations) or as monotherapy (with or without radiotherapy). Genotyping was originally only for *2A (275 patients), but from approximately 30% of the total study time genotyping for *13 and 2846A>T was added (214 patients) and from 65% of the total study time genotyping for 1236G>A was added (n = 109). Recommended dosing reduc- tions were 50% of the normal dose per *2A- and *13-variant and 25% per 1236A-variant. Recommended dosing reduction per 2846T-variant was 50% (change to a recommendation of 25% reduction was only after the study), but was not applied. 14 patients with gene variants were identified.	Authors' conclusion: 'Prospective DPYD screening can be implemented successfully in a real world clinical setting, is well accepted by physi- cians and results in low toxicity.'

		Due to the low number of nationte with DRD verients the study	
		was not newgrad to formally test the effect of genetype guided	
27101275.		desing on fluoronyrimiding induced toxicity and only explore	
rof 12 continua-		tive analyses could be performed	
tion		live analyses could be performed.	
uon		Constraine	
		- ΟΧ 1/1230A Σν *1/*2Λ	
		- JX I/ ZA 1 corrier of both *2A and 2946T (cither *2A/2946T (cn	
		-1 carrier of both 2A and 20401 (either 2A/20401 (off	
		Reculte:	
		$\sim 8$ patients (5x *1/1236A and 3x *1/*2A) received the	
		recommended initial dose reduction and did not develop	
		toxicity grade 3-4 in cycle 1	
		The dose of 4 patients was subsequently increased Two	
		patients (1x *1/1236A with a dose increase to 100% of	
		the normal dose and $1x *1/*2A$ with a dose increase to	
		60% of the normal dose) did not develop toxicity grade 3-	
		4. A patient with genotype *1/*2A developed diarrhoea	
		grade 3 and enteritis after dose increase to 80% of the	
		normal dose. Another patient with this genotype develo-	
		ped hand-foot-syndrome grade 2-3 after multiple cycles	
		with the normal dose.	
	AS 1.5: E	- 3 patients (1x *1/1236A and 2x *1/*2A) did not receive an	
	(2)#	initial dose reduction and developed toxicity grade 3-4 in	
		cycle 1. For two of these patients, therapy was started	
	AS 1: E	before the genotype was known. For the third patient, the	
	(2)#	oncologist did not reduce the dose, because the dose in	
		the chemotherapy regimen was already relatively low	
		(capecitabine plus radiotherapy).	
		For 1 patient with genotype *1/*2A, the dose was subse-	
		quently reduced to 50% of the normal dose and the	
		patient did not develop toxicity grade 3-4 anymore. The	
		other 2 patients quitted fluoropyrimidine therapy.	
		- For the carrier of both *2A and 28461, there was no dose	
		recommendation, because it was not known whether the	
		Variants were on different alleles or on the same allele.	
		Because therapy had to be started before the DPD-acti-	
	EENO on	vity would have been determined, the physician decided	
	50% of	to use a 50% dose reduction, taking into account the	
	the nor-	5 ELL containing regimens before. Elucropyrimiding there	
	mal dose.	ny was stopped in this patient after the first cycle due to	
	C (2) <sup>#</sup>	toxicity (< grade 3)	
	- (-)	- 2 patients (both with genotype *1/1236A) did not start	
		fluoropyrimidine therapy.	
ref. 13 – FU	3	A subset of patients from Lee 2014 was reanalysed: 1953	Authors' conclusion
comb	-	patients, negative for *2A. *13 and 2846T. and treated with 12	'No significant asso-
Lee AM et al.		cycles of adjuvant FOLFOX therapy (5-fluorouracil. folinic acid	ciations were identi-
Association		and oxaliplatin) with or without cetuximab. 62.9% of patients	fied between c.1129
between DPYD		had any grade $\geq$ 3 adverse event, with 32.7% having any	-5923 C>G/hapB3
c.1129-5923		grade $\geq$ 3 adverse event common to 5-fluorouracil treatment.	and overall grade≥3
C>G/hapB3 and		Adverse events classified as common to 5-fluorouracil treat-	adverse event rate.
severe toxicity to		ment were fatigue, anorexia, dehydration, diarrhoea, stomati-	Our results suggest
5-fluorouracil-		tis/mucositis, nausea/vomiting, leukopenia, neutropenia, febri-	that c.1129-5923
based chemothe-		le neutropenia, thrombocytopenia, and pain. Most frequent 5-	C>G/hapB3 have
rapy in stage III		fluorouracil adverse events included diarrhoea (12.5%), neu-	limited predictive
colon cancer		tropenia (10.3%), pain (5.4%), fatigue (5.2%), nausea/vomi-	value for severe
patients: NCCTG		ting (4.7%), and mucositis (4.1%).	toxicity to 5-FU-
NU147 (Alliance).		Results were adjusted for clinicopathological factors like age,	based combination
Pharmacogenet		sex, treatment, total number of treatment cycles and dose	chemotherapy.'

			ten terre este en el la la la mana en terre el	
Genomics		modifications. The lat	ter two outcomes (nigner percentage of	
2016;26:133-7.		patients with prematu	ire continuation and with dose modifica-	
PubMed PMID:		tion) might be results	of 5-fluorouracil adverse events instead	
26658227.		of causes.		
		Cetuximab increased	the risk of 5-fluorouracil adverse events.	
ref. 13. continua-		Results were adjusted	d for this. but this indicates that adverse	
tion		events common to 5-	fluorouracil are not the same as 5-fluoro-	
		uracil induced advers		
		Comotoria au		
		Genotyping:		
		- 1875x *1/*1		
		- 77x *1/1236A		
		- 1x 1236A/1236A		
		Results:		
		Risk of grade $\geq 3$ ad	verse event for 1236A/1236A versus	
		*1/1236A versus *1/	*1.	
		any adverse event	NS trend for an increase $(n = 0.082)$	
			$OD_{r}$ for (*1/1226A + 1226A/1226A)	
			$OR_{adj} IOI (1/1230A + 1230A/1230A)$	
			compared to 1/11 also showed a	
			trend for an increase (NS, $p = 0.127$ ).	
	AS 1.5 +	diarrhoea	NS	
	FENO: E	neutropenia	S for an increase	
		pain	NS	
		fatique	NS	
		nausea/vomiting	NS	
		stomatic/mucositic	NS	
		stomatis/mucositis	NG	
			NO NO	
		leukopenia	NS	
		NOTE: Results were	reported for 1129-5923C>G, which was	
		in complete linkage d	isequilibrium with the also genotyped	
		1236G>A.		
ref. 14 – FU/CAP,	3	1631 patients receive	d genotype-guided therapy with capeci-	Authors' conclusion:
mono/comb				Autions conclusion.
		tabine (90% of patien	ts) or 5-fluorouracil (10% of patients),	'DPYD*2A geno-
Deenen MJ et al.		tabine (90% of patien either as combined ch	ts) or 5-fluorouracil (10% of patients), nemotherapy (different combinations) or	'DPYD*2A geno- type-guided dosing
Deenen MJ et al. Upfront genoty-		tabine (90% of patien either as combined cl as monotherapy (with	ts) or 5-fluorouracil (10% of patients), nemotherapy (different combinations) or or without radiotherapy). Genotyping	'DPYD*2A geno- type-guided dosing results in adequate
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ref 14 continua.		- 18x *1/*2A					
tion							
		Posulte:					
		Treatment character	intion (	sf *1/**	A potionto:		
			isiles (	m 200	$\frac{2}{100}$ to $\frac{600}{100}$ of t	ha full daga	
		(modion 46%) The		111 297	o 10 00 % 01 1	7% to $01%$ of	
		(Ineulan 40%). The			aneu nom i		
		the full dose. The f			per treatmen	it cycle was	
		48% (range 17% to	591%)	. All pa	atients were	treated with	
		capecitabine.				1 000/ 1	
		- 5 patients develope	ed toxi	city gra	ade $\geq 3$ (first	cycle 29% to	
		60% of the normal	dose,	final c	ycle 17% to	60% and	
		maximum 2 <b>9</b> % to 6	67%)				
		- 2 patients develope	ed toxi	city gra	ade 0 (first o	f the two	
		cycles with 29% ar	nd seco	ond cy	cle with 59%	o of the nor-	
		mal dose and all five	ve cycl	es 489	% of the norr	nal dose,	
		respectively)					
		<ul> <li>11 patients develop</li> </ul>	ped to	kicity g	rade 1 to 2 (	first cycle	
		30% to 50% of the	norma	al dose	e, final cycle 2	24% to 91%	
		and maximum 46%	6 to 91	%)			
		- Toxicity was short	in dura	ition ai	nd well contr	olled using	
		standard supportiv	e care				
		- For 6 patients, the	dose v	vas ind	creased durir	ng treatment	
		(dose in first cycle	29% to	o 47%	of the norma	al dose; maxi-	
		mum dose 46% to	91%).				
		In two of these pat	ients (	dose ir	ncrease from	47% to 53%	
		and from 44% to 6	7%, rè	spectiv	vely), the dos	se was later	
		reduced to the initi	al dose	e adair	h because of	toxicity.	
		- For 3 patients, the	initial o	dose w	as still too h	igh and had	
		to be reduced furth	ner (init	ial dos	se 29% to 44	% of the	
		normal dose, final	dose 1	7% to	24%).		
		- Of 4 evaluable pati	ents. 2	achie	ved a partial	response	
		and 2 had stable d	isease				
		In 4 of 5 patients w	ith rec	tal car	ncer treated v	with chemo-	
		radiotherapy dowr	nstagin	a of th	e tumor fron	n pT3-4 to	
		vpT0-2 was reache	ed.	9			
		Percentage of *1/*2	A natie	nts wit	h toxicity for	reduced	
		dosing compared to	full do	sina.		leaded	
				sing.		value for	
						full do	
						iui uo-	
		any grada > 2 taviait		× 0 2	0 (0)	511 Y	
		any grade < 3 toxicit	у	x U.3	o (S)	13%	
				in ad	aition, the of	oserved toxi-	
				CITY V	vas snort in (		
				reau	ced dosing a	nd usually	
				iong-			
		grade ≥ 3 haematolo	ogical	x 0.2	o (S)	66%	
		toxicity			. (2)		
		grade ≥ 3 gastrointe	stinal	x 0.2	U (S)	56%	
		toxicity					
		tluoropyrimidine-indu	uced	NS		10%	
		death					
		Percentage of patier	nts with	n toxici	ity for *1/*2A	on reduced	
		dosing compared to	*1/*1 c	on full	dosing:		
						value for	
						*1/*1	
	AS 1 on	any toxicity	grade	e ≥ 3	NS	23%	
	48% of		grade	e 1-2	NS	54%	
	the nor-	haematological	grade	e ≥ 3	NS	10%	
	mal dose.	toxicity	grade	e 1-2	NS	35%	
	AA	diarrhoea	grade	e ≥ 3	NS	8%	
		Jannoou	grade	- <u></u> - 1-2	NS	29%	
			graue	- 1 <sup>-1</sup> -		2070	

ref. 14. continua-		hand-foot syn-	orade ≥ 3	NS	5%	
tion		drome	grade 1-2	NS	28%	
		The authors indicate	that the com	narable toxicit	v burden	
		suggests that *1/*2A	is not under	exposed when	treated	
		with a median dose	of 48%		lioutou	
		with a median dooc	01 40 /0.			
		Dose normalised ph	armacokineti			
		activity for *1/*2A co	mpared to *1		izyine	
				/ 1.	volue for	
					value 101 *1/*1	ALIC versus AS 2:
		5 fluorourooil ALIC n	ormoliood	x 2.02 (NS)	602	ΔS 1· 203%
	AS 1: A	to a consoitabing do		x 2.03 (NS)	002 ng h/ml	AO 1. 20070
			se 01 1250		ng.n/m	
		DDD onzyma ootiyity	, in	x 0.64 (S)	0.0 pmol/	
		poriphoral monopula	y III Ioar blood	x 0.04 (S)	9.9 mmol/	
					ni per ng	
	4	Mete enclusio of 9 oc	hartatudiaa u	vith in total 720	protein E notionto	Authors' conclusions
ref. $15 - FU/CAP$ ,	4	treated with 5 flueres	nonstudies w	/itn in total 730	o patients	Authors conclusion:
Mono/comb		Irealed With 5-Iluorou	racii or caped	citabine, either	as complhed	DPYD variants
ivieuienaijks D et		chemotherapy (differe	ent compinati	ons) or as mor	notherapy	c.16791>G and
al.			nerapy).	•••••!:••••••••••••••		C. 1230G>A/HapB3
		Data on "13 were der	ived from 5 s	tudies includin	g a total of	are clinically rele-
		5,616 patients and 11	carriers of *	13. Data on 12	36G>A were	fuerenvrimidine
C.10/91/G,		derived from 6 studies	s including a	total of 4,261 p	batients and	nuoropynmiaine-
C. 1230G-A/Hapb		1/4 heterozygous car	rriers and 3 h	omozygous ca	irriers of	Linfront corooning
5, and C. 160 IG-A		1236A. Data on *2A v	vere derived	from 7 studies	including a	for those verients in
as predictors of		total of 5.737 patients	and 60 carri	ers of *2A. Dat	a on 2846	addition to the este
rimidino oppopio		A>T were derived from	m all 8 studie	s including a to	otal of 7,318	blichod voriante
ted toxicity: a		patients and 85 carrie	ers of 2846T.			DISTIEU Variants
systematic review		1 of the 8 studies in the	nis meta-ana	lysis is also inc	luded in the	
and meta analysis		meta-analysis of Ros	marin 2014 (l	Rosmarin 2014	<ol> <li>2 of the 8</li> </ol>	commended to im
of individual na-		studies in this meta-a	nalysis are a	lso included in	the meta-	prove the safety of
tient data		analysis of Terrazzino	o 2013 (More	I 2006 and De	enen 2011).	natients with cancer
Lancet Oncol		5 of the 8 studies in the	nis meta-anal	lysis are also iı	ncluded sepa-	treated with fluoro-
2015 16 1639-50		rately in this risk anal	ysis: Morel 20	006, Deenen 2	011, Lee	nvrimidines '
PubMed PMID		2014, Rosmarin 2014	and Meulen	dijks 2017.		pyrinnanios.
26603945		If possible, a RR was	calculated for	or each study b	ased on indi-	
20000010.		vidual patient data an	d adjusted fo	r age, sex, and	d treatment	
		regimen. For 2 of the	5 studies for	*13, it was not	possible to	
		use individual patient	data. A rand	om-effects mo	del was used	
		for the meta-analysis.				
		Haematological toxici	ty included th	rombocytoper	iia, neutro-	
		penia, leukocytopenia	a, and anaem	ia. Gastro-inte	stinal toxicity	
		included diarrhoea. m	ucositis/stom	natitis. and nau	sea/vomiting.	
		Short timeframe was	defined as sh	norter than the	complete	
		treatment duration. lo	ng timeframe	as the whole	treatment	
		duration.	5			
		In addition, a meta-ar	nalvsis of 3 ca	ase-control stu	dies with in	
		total 799 patients was	s performed f	or 1236G>A	)ne of these	
		case-control studies i	s also include	ed in the meta-	analysis of	
		Rosmarin 2014 (Schu	vab 2008) an	d two in the m	eta-analysis	
		of Terrazzino 2013 (S	Chwab 2000) dh	and Kleihl 200	(a) One of	
		these case-control st	idies is also i	included senar	ately in this	
		rick analysis (Schwah	2008)			
		Results:				
		Risk of grade > 3 to	vicity for *1/*1	3 compared to	) *1/*1·	
					inciden-	
					ce for	
			RRadi (9	5% CI)	*1/*1 (%	
					of pa-	
					tients)	
	AS 1: F	any toxicity	4 40 (2 (	08-9 30) (S)	22%	
L	, .o L		2.0 (2.0	55-5.507 (5)	LL /U	1

<b>6 4 - 4</b>				<u> </u>	-
tion		haematological toxi- city	9.76 (3.03-31.48) (S)		
		gastrointestinal toxi-	5.72 (1.40-23.33) (S)		
		band fact syndrome	(PP could not be cal		
		hand-loot syndrome	culated due to an inci-		
			dence of $0\%$ in $*1/*13$ )		
		The heterogeneity betw	veen the studies was signi	ficant and	
		substantial, possibly be	cause of the small numbe	er of	
		*1/*13.			
		There was no indication	n of publication bias.		
		The results for any toxic	city were similar when pat	ients	
		carrying "ZA and/or 284	to I were excluded from in	th n <	
		0.0167 after exclusion (	of any study from the met	a-analysis	
		except for Loganavaga	m 2013. After exclusion of	f Loga-	
		nayagam 2013, the p-v	alue was 0.0433.	J II	
		The effect of *13 on risl	k of severe toxicity seeme	d similar	
		in studies with long and	I short timeframes.		
		The sensitivity of *13 in	prediction of grade $\geq$ 3 to	xicity was	
		0.3% and the positive p	predictive value 46%.		
		Pick of grade > 3 toxicit	$h_{1}$ for (*1/1026A $\pm$ 1026A/2	12264)	
		compared to $*1/*1$	IN 101 ( 1/1230A + 1230A)	1230A)	
				inciden-	
				ce for	
			RR <sub>adj</sub> (95% CI)	*1/*1 (%	
				of pa-	
	AS 1.5 +			tients)	
	FENO: E	any toxicity	1.59 (1.29-1.97) (S)	22%	
		haematological toxi-	2.07 (1.17-3.68) (S)		
		CITY controlational toxi	2.04 (1.40.2.79) (8)		
		city	2.04 (1.49-2.76) (3)		
		hand-foot syndrome	NS (also for the sub-		
			group treated with		
			capecitabine)		
		There was no significar	nt heterogeneity between t	the stu-	
		There was no indication	a of publication bias		
		The results for any toxic	city were similar when pat	ients	
		carrying *2A and/or 284	16T were excluded from th	ne meta-	
		analysis. The association	on remained significant af	ter exclu-	
		sion of any study from t	the meta-analysis.		
		The effect of 1236A on	risk of severe toxicity see	med simi-	
		lar in studies with long a	and short timetrames.		
		The sensitivity of 1236	A in prediction of grade $\geq 3$	3 toxicity	
		The meta-analysis of th	ne case-control studies did	I not show	
		a significant result, prot	bably due to the smaller n	umber of	
		patients.	,		
		The authors reported to	have treated 3 patients v	vith geno-	
		type 1236A/1236A safe	ely with low dose capecital	bine (825	
		_ mg/m² twice a day).			
		Pick of grade > 2 toyicit	hy for *21 corriers compar	ed to	
		*1/*1:	ly for ZA-camers company		
				inciden-	
				ce for	
			RR <sub>adj</sub> (95% CI)	*1/*1 (%	
				tients)	
		L	I		

ref. 15, continua-		any toxicity	2.85 (1.75-4.62) (S)	29%	
tion		The heterogeneity betw	een the studies was signi	ficant and	
		strong.	of publication biog		
			T OI PUDIICATION DIAS.		
		Risk of grade ≥ 3 toxicit	ty for 2846T-carriers comp	pared to	
		*1/*1:			
				inciden-	
			BBadi (95% CI)	Ce for *1/*1 (%	
				of pa-	
				tients)	
	AS 1.5: E	any toxicity	3.02 (2.22-4.10) (S)	25%	
		I he heterogeneity betw	leen the studies was signi	ficant and	
		There was no indication	n of publication bias.		
		NOTE: 1236G>A is in co	mplete linkage diseguilibr	ium with	
		1129-5923C>G in haplot	type B3. Studies analysing	both gene	
		variants were pooled.			
		NOTE: Meta-analysis of	5 studies with in total 390	0 patients,	
		182x *1/*4 and $2x *4/*4$ , between *4 and grade >	showed no significant ass 3 toxicity. The only study	ociation	
		significant effect (Logana	ayagam 2013) was the car	use of	
		strong heterogeneity bet	ween the studies. In addit	ion, results	
rof 16 - Ell	3	regarding the effect of *4	on DPD activity are incor	nsistent.	Authors' conclusion:
comb	5	FOLFOX therapy (5-fluor	rouracil. folinic acid and o	ant xaliplatin:	Statistically signifi-
Lee AM et al.		91.9% of patients) or FO	LFIRI therapy (5-fluoroura	acil, folinic	cant associations
DPYD variants as		acid and irinotecan; 8.1%	6 of patients) with or with	out cetuxi-	were found between
fluorouracil toxici-		wed by six cycles of FOL	FIRI with or without cetux	rox iolio- imab.	(DPYD*2A and
ty in adjuvant co-		62.0% of patients had ar	ny grade $≥$ 3 adverse ever	it, with	2846A>T) and
lon cancer treat-		33.1% having any grade	≥ 3 adverse event commo	on to 5-	increased incidence
N0147)		diuorouracii treatment.	d as common to 5-fluorou	racil treat-	5FU-adverse events
J Natl Cancer Inst		ment were fatigue, anore	exia, dehydration, diarrhoe	a, stomati-	in patients treated
2014;106:dju298.		tis/mucositis, nausea/vor	miting, leukopenia, neutro	penia, fe-	with adjuvant 5-FU-
PubMed PMID:		brile neutropenia, thromb	pocytopenia, and pain. Mo vents included diarrhoea (	st frequent	based combination
20001090.		neutropenia (11.7 %), na	usea/vomiting (5.0%), fat	ique (4.9%),	chemotherapy.
		and mucositis (4.2%).	<b>U</b> (1)	5 ( - //	
		Follow-up for disease fre	e survival was for 5 years		
		Results were adjusted to sex treatment total num	or clinicopathological facto	rs like age, nd dose	
		modifications. The latter	two outcomes (higher per	centage of	
		patients with premature of	continuation and with dose	e modifica-	
		tion) might be results of t	5-tluorouracil adverse eve	nts instead	
		Cetuximab increased the	e risk of 5-fluorouracil adve	erse events.	
		OR's were adjusted for the	his, but other outcomes w	ere not. In	
		addition, this indicates the	at adverse events commo	on to 5-fluo-	
		events.		auveise	
		Genotypina:			
		- 2532x *1/*1			
		- 24x *1/*2A			
		- 26X ^1/28461  - 1x *2Δ/2846T			
		- 1x *1/274C			
		- 5x *2A-genotyping faile	d		

ref. 16, continua-		- 5x 2846A>T-genotyping	g failed		
tion		0 11			
		Results:			
		Risk of grade ≥ 3 toxicit	v. premature treatment te	rmination	
		and disease free surviv	al for *2A-carriers compar	ed to non-	
		carriers:	·		
				inciden-	
				ce for	
				non-	
				carriers	
		any toxicity	OR <sub>adi</sub> = 3.58 (95% CI:	62%	
		5 5	1.01-12.64) (S)		
	AS 1 +	any 5-FU toxicity	OR <sub>adi</sub> = 14.91 (95% CI:	33%	
	FENO: E	J = _ J	4.26-52.18) (S)		
		diarrhoea	NS	12%	
		neutropenia	x 5 7 (S)	11%	
		nausea/vomiting	x 4 2 (S)	4.8%	
		fatique	NS	4.8%	
		stomatitis/mucositis	NS trend for an	4.2%	
		Stornatilio, madoosilio	increase $p = 0.09$	4.270	
		dehydration	NS	2.3%	
		leukopenia	NS trend for an	1.8%	
			increase. $p = 0.08$	1.070	
		febrile neutropenia	NS trend for an	1.6%	
		·····	increase, $p = 0.07$		
		anorexia	NS	1.5%	
		nain	NS	0.8%	
		thrombocytopenia	NS trend for an	0.3%	
		anombooytoponia	increase $p = 0.08$	0.070	
		premature treatment	x 1 7 (S)	26%	
		termination			
		dose modification	NS	74%	
		disease free survival	NS	73%	
		after 3 year			
		When restricting the an	alysis to Caucasians, sex	or treat-	
		ment, the association b	etween *2A and grade ≥ 3	3 5-FU	
		toxicity remained signifi	cant, whereas the associa	ation	
		between *2A and grade	≥ 3 overall toxicity did no	t.	
		Risk of grade $\geq$ 3 toxicit	y, premature treatment te	rmination	
		and disease free surviv	al for *2846T-carriers cor	npared to	
		non-carriers:			
				inciden-	
				ce for	
				non-	
				carriers	
		any toxicity	UR <sub>adj</sub> = 5.43 (95% CI: 1.52-19.43) (S)	62%	
	AS 1.5 +	any 5-FU toxicity	$OR_{adj} = 10.24 (95\% CI:$ 3 57-29 40) (S)	33%	
		diarrhoea	x 2 8 (S)	12%	
		neutropenia	x 4 9 (S)	11%	
		nausea/vomiting	NS	5.0%	
		fatique	NS	4.8%	
		stomatitie/mucositie	NS	4.0%	
		dehydration	x 5 0 (S)	<u>+.1/0</u> 2.2%	
			x 8.0 (0)	<u>2.2/0</u> 1.8%	
		febrile noutrononia	$\Lambda 0.2 (0)$	1.0 /0	
			increase $n = 0.02$	1.0 /0	
		anorexia	NS	1.5%	
		nain	NS	0.8%	
		thrombocytonenia	x 55 5 (S)	0.0%	
		апопросуюрениа	<u> </u>	0.2/0	1

ref. 16 continua-		premature treatment	NS	26%	
tion		termination		2070	
		dose modification	NS	74%	
		disease free survival	NS	73%	
		after 3 year	alvoia ta Caucasiana, ao	v or troot	
	FENO: F (2)#	<ul> <li>When restricting the arment, the association be toxicity remained signif 2846T and grade ≥ 3 of the subgroups of Cauce subgroups of females, ximab.</li> <li>Other results: <ul> <li>Because of its low free association could not either 5-FU or overall</li> <li>The *2A/2846T-patient patient was only able cetuximab.</li> <li>The *1/274C-patient I</li> </ul> </li> </ul>	halysis to Caucasians, sepetween 2846T and grad ficant. The association be overall toxicity remained s asians and males, but no FOLFOX only and FOLF equency, a statistically sig be demonstrated between grade $\geq$ 3 toxicity (NS). In had a grade 5 adverse to receive one cycle of F had no grade $\geq$ 3 adverse	ex or treat- e $\geq$ 3 5-FU etween significant in of in the FOX + cetu- gnificant en *13 and event. The FOLFOX +	
		<ul> <li>The gene variants *2/ ted 5-FU grade ≥ 3 to specificity of 99.4%, µ and negative predicti and negative predicti combination chemoth toxicity.</li> </ul>	A, *13 and 2846A>T toge oxicity with a sensitivity of oositive predictive value of ve value of 68%. The low ve value might be attribu- nerapy, which may add to	ether predic- f 5.3%, of 81.8% v sensitivity ted to the o the 5-FU	
		NOTE: Genotyping was (*2A, *13, 2846G>T and lation from the USA.	for 25 gene variants of w I 274G>C) were found in	vhich only 4 this popu-	
ret. 17 – CAP/FU, comb Rosmarin D et al. Genetic markers of toxicity from capecitabine and other fluorouracil- based regimens: investigation in the QUASAR2 study, systematic review, and meta- analysis. J Clin Oncol 2014;32:1031-9. PubMed PMID: 24590654.		After colorectal cancer e vant therapy with capec days 1-14 of a 3-week c or in combination with b toxicity comprised hand = 97) and neutropenia (n Variant 2846A>T: - Associated with grade 2.01-43.4) (S) - No association with gra hand-foot syndrome (N Given the allele freque 5 defect alleles. Variants *2A, 496A>G, 7 - No association with gra and grade III-V hand-fo Given the allele freque 4 defect alleles for *2A	excision, 927 patients rec itabine 1250 mg/m <sup>2</sup> twice eycle either as monothera evacizumab (n = 491). G foot syndrome (n = 206) n = 19). III-V toxicity (OR = 9.35; ade III-V diarrhoea and g NS). ency found, this is appare 1236G>A: ade III-V toxicity, grade II pot syndrome (NS). ency found, this is appare A, 83 for 496A>G and 18	eived adju- e daily on py (n = 436) rade III-V , diarrhoea (n 95% CI: rade III-V ently based on I-V diarrhoea ently based on for 1236G>A.	Autnors' conclusion: "Global capecitabine toxicity (grades 0/1/2 v grades 3/4/5) was associated with the rare, functional DPYD alleles 2846T>A and *2A (combined odds ratio, 5.51)."
	AS 0-1.5 + FENO: E	Variant 2846A>T and/or - Associated with grade 1.95-15.5) (S) - No association with gra hand-foot syndrome (N - Both patients who diec Meta-analysis of 6 studi	**2A: III-V toxicity (OR = 5.51; ade III-V diarrhoea and g NS) I were carriers of *2A or 2 es during which Caucasia	95% CI: rade III-V 2846A>T an patients	

ref 17 continua-		6 studies, the study covered in the paragraph above and	
tion		Schwab 2008 were also included separately in this risk	
		analysis	
		analysis.	
		Variant *2A	
		No association with grade III V toxicity for canecitabine (2	
		studies $n = 1035$ (NS)	
		No significant association with grade IILV toxicity for fluoro-	
		uracil infusion, but there was a trend (2 studies, $n = 732$ )	
		(NS: $n = 0.0075$ whilst this should be less than 0.0048 due	
		to multiple testing)	
		- No significant association with grade III-V toxicity for fluoro-	
		uracil bolus injection, but increased risk of grade III-V neutro-	
		penia (OR = 12.9: 95% CI: 3.13-53.3) (1 study. n = 338) (S)	
		Variant 2846A>T:	
		- No meta-analysis for capecitabine, fluorouracil infusion and	
		fluorouracil bolus injection (1 study each time)	
		Variant 496G>A:	
		- No meta-analysis for capecitabine and fluorouracil infusion	
		(in both cases only 1 study)	
		- No association with grade III-V toxicity for fluorouracil bolus	
		injection (2 studies, n = 379) (NS)	
		Variant 1236G>A:	
		- No meta-analysis for capecitabine, fluorouracil infusion and	
		fluorouracil bolus injection (1 study each time)	
		Variant 2846A>T and/or *2A:	
		- No meta-analysis for capecitabine (only 1 study)	
		- There was a significant association (p = 0.05) with grade III-	
		V toxicity for fluorouracil infusion and fluorouracil bolus injec- tion (S)	
		NOTE: No association was found for the gene variants *4 *5	
		*6 and *9A. However, associations with severe toxicity have	
		never been found in studies concerning these gene variants.	
ref. 18 - FU/CAP,	4	Meta-analysis of 15 studies investigating patients treated with	Authors' conclusion:
mono/comb		fluorouracil, capecitabine or tegafur-uracil (1 study). Data on	"The results of this
Terrazzino S et al.		*2A (IVS14+1G>A) were derived from 15 studies including a	meta-analysis con-
DPYD IVS14+1		total of 4,094 patients and 60 carriers of *2A. Data on 2846	firm clinical validity
G>A and 2846		A>T were derived from 7 studies including a total of 2,308	of DPYD IVS14+1
A>1 genotyping		patients and 34 carriers of 2846A>T. These 15 studies include	G>A and 2846A>1
of severe fluoro		8 studies that have also been included separately in this risk	the development of
ovrimidine-related		analysis: Salgueiro 2004, Morel 2006, Largillier 2006, Bois-	severe toxicities
toxicity: a meta-		dron-Celle 2007, Schwab 2008, Sulzyc-Bielicka 2008, Kristen-	following fluoropyri-
analysis.		sen 2010 and Deenen 2011.	midine treatment."
Pharmacogeno-		*24 versus (no $*24$ ):	
mics		$\Delta A$ versus (IIO $\Delta A$ ).	
2013;14:1255-72.	45 1· E	2 79-10 52' increase in the percentage of patients with grade	
PubMed PMID:	AG 1. L	III-V toxicity from 39% to 68%) (S)	
23930673.		Exclusion of each of the studies from the meta-analysis did	
		not lead to substantially different results (OR = 4.05 - 7.32	
		(S)).	
		The risk was increased in studies in which the percentage of	
		patients with grade III-V toxicity was less than 40% (OR =	
		0.31, 95% UI: 3.03-19.06) (S). However, the increase was	
		non-significant in studies including $\geq$ 40% of patients with toxicity	
		luxicity.	

ref. 18, continua-		The results were similar if only prospective studies, only	
tion		higher quality studies or only studies including $\geq$ 200 patients	
		were analysed. In prospective studies, the risk also increa-	
		sed as the incidence of grade III-V toxicity decreased in the	
		study.	
		The risk was also increased when only studies investigating	
		fluorouracil-based therapy or fluorouracil monotherapy were	
		analysed.	
		<ul> <li>Increased risk of grade III-V haematological toxicity (OR =</li> </ul>	
		15.77; 95% CI: 6.36-39.06) (S)	
		- Increased risk of grade III-V diarrhoea (OR = 5.54; 95% CI:	
		2.31-13.29) (S)	
		- Increased risk of grade III-V mucositis (OR = 7.48; 95% CI:	
		3.03-18.47) (S)	
		- *2A had a sensitivity of 5.2% (95% CI: 3.0-8.9) and a speci-	
		ficity of 99.2% (95% CI: 98.8-99.4) for predicting grade III-V	
		toxicity (S)	
		The sensitivity was 9.0% for studies that showed less than	
		40% grade III-V toxicity (95% CI: 5.7-13.9) (S).	
		There was study heterogeneity in the overall group, but not	
		in the group with less than 40% toxicity.	
		- *2A had a sensitivity of 13% (95% CI: 6.6-24.1) for predicting	
		grade III-V haematological toxicity (S)	
		- *2A had a sensitivity of 5.6% (95% CI: 3.2-9.7) for predicting	
		grade III-V diarrhoea (S)	
		- *2A had a sensitivity of 11.5% (95% CI: 6.2-20.5) for predic-	
		ting grade III-V mucositis (S)	
		2846A>T versus (no 2846A>T):	
	AS 1.5: E	- Increased risk of grade III-V toxicity (OR = 8.18; 95% CI:	
		2.65-25.25; increase in the percentage of patients with grade	
		III-V toxicity from 34% to 71%) (S)	
		Exclusion of each of the studies from the meta-analysis did	
		not lead to substantially different results (OR = 6.20 - 12.88	
		(S)).	
		The risk was increased in studies in which the percentage of	
		patients with grade III-V toxicity was less than 40% (OR =	
		16.59; 95% CI: 5.06-54.43) (S). However, the increase was	
		non-significant in studies including ≥40% of patients with	
		toxicity.	
		The results were similar if higher only quality studies or only	
		studies including $\geq$ 200 patients were analysed.	
		The risk was also increased when only prospective studies	
		were analysed (OR = 18.14; 95% CI: 6.26-52.58) (S) or only	
		studies investigating fluorouracil-based therapy (OR = 21.38;	
		95% CI: 6.71-68.15) (S).	
		There was moderate study heterogeneity in the overall	
		group, but not in the low or high toxicity subgroups, among	
		prospective studies or among those investigating fluoroura-	
		cil-based therapy. There may have been publication bias.	
		- Increased risk of grade III-V diarrhoea (OR = 6.04; 95% CI:	
		1.77-20.66) (S)	
		- 2846A>T had a sensitivity of 5.4% (95% CI: 1.7-16.1) and a	
		specificity of 99.1% (95% CI: 98.7-99.4) for predicting grade	
		III-V toxicity (S)	
		The sensitivity was 11.2% for studies that showed less than	
		40% grade III-V toxicity (95% CI: 2.8-35.1) (S).	
		I nere was neterogeneity between the studies.	
		-2040A>1 nad a sensitivity of 4.0% (95% CI: 2.2-9.4) for	
rof 10 ELUCAD	2	predicting grade III-v diarmoea (5)	Authora' conclusion
$\frac{1}{100} = \frac{1}{100} = \frac{1}$	2	and neck tumours received fluorouracil or conscitation head	"Our data suggest
Magnani F et al		therapy (adjugant or metastatic therapy) A 4 <sup>th</sup> patient with	that greater dose re-
magnam E ot al.		I merapy (aujuvani or merasiano merapy). A 4 paneni willi	

Fluoropyrimidine toxicity in patients with dihydropy- rimidine dehydro- genase splice site variant: the need for further revision of dose and sche- dule. Intern Emerg Med 2013;8:417-23. PubMed PMID: 23585145. <b>ref. 19, continua- tion</b>	AS 1: E	<ul> <li>genotype *1/*2A was not given adjuvant therapy.</li> <li>A 43-year-old colon cancer patient was given adjuvant therapy with capecitabine/oxaliplatin and a 50% dose of capecitabine (500 mg/m<sup>2</sup> twice daily for 14 days, followed by a weeklong rest period). The patient developed diarrhoea, grade 4 neutropenia and grade 3 thrombocytopenia after 19 days. The adjuvant therapy was discontinued.</li> <li>A 71-year-old colon cancer patient received the same adjuvant therapy including 40% of the normal capecitabine dose (400 mg/m<sup>2</sup> twice daily). After 1 day, the patient started vomiting and developed grade 3 abdominal pain. The adjuvant therapy was discontinued.</li> <li>A 68-year-old patient with metastatic maxillary sinus cancer initially received fluorouracil/carboplatin/folinic acid with standard-dose fluorouracil (3000 mg/m<sup>2</sup> continuous infusion + 400 mg/m<sup>2</sup> bolus every 3 weeks). After 15 days, he developed grade 4 neutropenia and thrombocytopenia, and grade 3 sepsis and ulceration of the palate. After recovery, the treatment was restarted at 44% of the original dose (1500 mg/m<sup>2</sup> bolus) and no growth factors were given. After 14 days, the patient developed grade 4 febrile neutropenia and grade 2 anaemia. He was henceforth given non-fluoropyrimidine-based therapy.</li> </ul>	ductions or alterna- tive therapies are needed for patients with DPD IVS14+1 G>A mutations."
<b>ref. 20 – FU,</b> <b>comb</b> Vulsteke C et al. Genetic variability in the multidrug resistance asso- ciated protein-1 (ABCC1/MRP1) predicts hemato- logical toxicity in breast cancer patients receiving (neo-)adjuvant chemotherapy with 5-fluoroura- cil, epirubicin and cyclophospha- mide (FEC). Ann Oncol 2013;24:1513-25. PubMed PMID: 23396606.	4 AS 1: AA	<ul> <li>1012 breast cancer patients received neoadjuvant/adjuvant therapy with fluorouracil, epirubicin and cyclophosphamide. The fluorouracil dose was 500 mg/m<sup>2</sup> every 3 weeks with a maximum of 1000 mg (n=902) or 600 mg/m<sup>2</sup> with a maximum of 1200 mg (n = 110).</li> <li>Variant *2A (c.1905+1G&gt;A, rs3918290): <ul> <li>No significant association with serious adverse events (febrile neutropenia, prolonged grade III-IV neutropenia or severe neutropenia, grade III-IV anaemia, grade III-IV thrombocytopenia or grade III-IV non-haematological toxicity) (NS)</li> </ul> </li> <li>The authors indicated that the lack of association is likely due to the fact that fluorouracil toxicity is not common among breast cancer patients treated with this combination therapy. The fluorouracil dose in this combination therapy is much lower than the dose in combination therapies used for colorectal cancer.</li> <li>NOTE: Associations were also not found for gene variants *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C). However, associations with severe toxicity have never been found in studies concerning these gene variants.</li> </ul>	Authors' conclusion: "In our study, we did not observe any association with toxicity and IVS14+1 G>A. The absence of a significant asso- ciation with IVS14+1 G>A probably rela- tes to the fact that 5- FU toxicity is not frequent in breast cancer patients trea- ted with FEC due to a much lower 5-FU dose in breast com- pared with colorectal cancer patients."
<b>ref. 21 – FU,</b> <b>mono/ comb</b> van Kuilenburg AB et al. Evaluation of 5- fluorouracil phar- macokinetics in cancer patients with a c.1905+1	3	<ul> <li>Clinical aspects were determined in 20 patients who had been genotyped as *1/*2A beforehand and were treated with fluoro-uracil. Kinetics were determined in 30 *1/*2A (c.1905+1G&gt;A) and 18 *1/*1, who received a fluorouracil bolus injection of 300 mg/m<sup>2</sup> and/or 450 mg/m<sup>2</sup>. Treatment regimens were not given.</li> <li><i>Clinical</i></li> <li>All 7 *1/*2A receiving a standard dose of fluorouracil showed grade III-V toxicity, of which 3 showed grade IV neutropenia</li> </ul>	Authors' conclusion: "Profound differen- ces in the elimina- tion of 5FU could be detected between DPD-deficient patients and control patients. Furthermore, treat-

G>A mutation in DPYD by means of a Bayesian limited sampling strategy. Clin Pharmaco- kinet 2012;51:163-74. BubMed BMID:	AS 1: F	<ul> <li>The severe toxicity occurred in the first cycle each time and 1 patient died.</li> <li>Among 13 *1/*2A receiving low-dose fluorouracil, 4 had grade III toxicity and none had grade IV toxicity.</li> <li>The patients with grade III toxicity received on average 74% of the standard dose, and those with grade II or lower toxicity received 61% of the dose.</li> </ul>	ment of DPD-defi- cient patients with standard 5FU-con- taining chemothera- py was associated with severe (lethal) toxicity."
ref. 21, continua-		Kinetics *1/*2A versus *1/*1: - The fluorouracil AUC increased by 52% for the 300 mg/m <sup>2</sup> dose (from 6.0 to 9.1 mg.hour/L) and by 32% for the 450 mg/m <sup>2</sup> dose (from 13.4 to 17.7 mg.hour/L) (S)	Maximum clearance (V <sub>max</sub> for 300 mg/m <sup>2</sup> ) versus AS 2: AS 1: 54%
		The dose-corrected AUC increased by 32% (from 0.026 to 0.034 mg.hour/L per mg/m <sup>2</sup> ; 45 and 25 patient/dose combinations respectively) (S). The AUC seems to be predictive of the first 2 hours after the injection and may therefore cause an underestimate for *1/*2A. The fluorouracil concentration 1 hour after injection was around the detection limit for *1/*1.	AUCt versus AS 2: AS 1: 132%
		<ul> <li>the 300 mg/m<sup>2</sup> dose (from 0.128 to 0.268 hours) and by 69% for the 450 mg/m<sup>2</sup> dose (from 0.181 to 0.306 hours) (S)</li> <li>The maximum enzymatic metabolic capacity (V<sub>max</sub>) calculated in a multi-compartment model decreased by 46% for the 300 mg/m<sup>2</sup> dose (from 1749 to 942 mg/hour) and by 34% for the 450 mg/m<sup>2</sup> dose (from 1370 to 900 mg/hour) (S)</li> </ul>	
ref. 22 – CAP, comb Deenen MJ et al. Relationship between single nucleotide poly- morphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in	4	<ul> <li>568 patients with advanced colorectal cancer were treated with capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks, in combination with oxaliplatin and bevacizumab, with or without cetuximab. Oxaliplatin was discontinued from cycle 7 and the capecitabine dose increased to 1250 mg/m². Grade III-IV toxicity occurred in 85% of the patients.</li> <li>*1/*2A versus *1/*1:</li> <li>Factor 3.0 increase in the percentage of patients with grade III-IV diarrhoea (from 24% to 71%) (S; strong association: false discovery rate &lt; 0.3)</li> </ul>	Authors' conclusion: "Of the patients po- lymorphic for DPYD IVS14+1G>A, 2846 A>T, and 1236G>A, 71% (5 of 7), 63% (5 of 8), and 50% (14 of 28) developed grade 3 to 4 diar- rhea, respectively, compared with 24%
advanced colo- rectal cancer. Clin Cancer Res 2011;17:3455-68. PubMed PMID: 21498394.	AS 1: F	<ul> <li>The sensitivity of *2A for predicting grade III-IV diarrhoea was 4% and the specificity 100%.</li> <li>No increase in the percentage of patients with grade II-III hand-foot syndrome and no significant increase in the percentage of patients with grade III-IV toxicity (NS) All 7 *1/*2A developed grade III-IV toxicity (including 3 women), and 1 patient died during the 3<sup>rd</sup> cycle.</li> <li>Decrease in the cumulative dose over the first 6 cycles (S): the average dose decrease increased from 10% to 51% in</li> </ul>	in the overall popu- lation. DPYD IVS14+1G>A and 2846A>T pre- dict for severe toxi- city to capecitabine, for which patients require dose reduc- tions
	AS 1.5 + FENO: E	<ul> <li>the lowest-dose cycle and from 10% to 44% in cycle 6.</li> <li>No difference in mortality or progression-free survival (NS)</li> <li>(*1/1236A + 1236A/1236A) versus *1/*1:</li> <li>Factor 2.2 increase in the percentage of patients with grade III-IV diarrhoea (from 23% to 50%) (S; strong association: false discovery rate &lt; 0.3)</li> <li>The sensitivity of 1236G&gt;A for predicting grade III-IV diarrhoea was 10% and the specificity 97%.</li> <li>No significant increase in the percentage of patients with grade III-III hand-foot syndrome or with grade III-IV toxicity (NS).</li> <li>No significant increase in dose decreases (NS)</li> </ul>	The data suggest that initial dose reductions of 50% in IVS14+1 G>A and 25% in 2846A>T va- riant allele carriers with further dose titration would signi- ficantly reduce the total number of se- vere toxicity events, thereby separate validation is indica-

ref. 22. continua-			ted."
tion		*1/2846T versus *1/*1:	
		- Factor 2.6 increase in the percentage of patients with grade	
	AS 1.5: E	III-IV diarrhoea (from 24% to 62%) (S: medium association:	
		false discovery rate 0.3-0.4)	
		The sensitivity of 2846A>T for predicting grade III-IV diar-	
		rhoea was 4% and the specificity 99%.	
		- No significant increase in the percentage of patients with	
		grade II-III hand-foot syndrome or with grade III-IV toxicity	
		(NS).	
		- Decrease in the cumulative dose over the first 6 cycles (S):	
		the average dose decrease increased from 10% to 27% in	
		the lowest-dose cycle and from 10% to 24% in cycle 6.	
		- No difference in mortality or progression-free survival (NS)	
		, , , , , , , , , , , , , , , , , , , ,	
		(*1/*6 + *6/*6) versus *1/*1:	
		- Factor 1.8 increase in the percentage of patients with grade	
		III-IV diarrhoea (from 23% to 41%) (S; medium association:	
		false discovery rate 0.3-0.4)	
		The sensitivity of *6 (2194G>A) for predicting grade III-IV	
		diarrhoea was 12% and the specificity 95%.	
		- No significant increase in the percentage of patients with	
		grade II-III hand-foot syndrome or with grade III-IV toxicity	
		(NS).	
		- No significant increase in dose decreases (NS)	
		- No difference in mortality or progression-free survival (NS)	
		(*1/496G + 496G/496G) versus *1/*1:	
		- Factor 1.4 increase in the percentage of patients with grade	
		III-IV diarrhoea (from 23% to 33%) (S; weak association:	
		false discovery rate < 0.3)	
		The sensitivity of 496A>G for predicting grade III-IV diar-	
		rhoea was 24% and the specificity 84%.	
		- Factor 1.3 increase in the percentage of patients with grade	
		II-III hand-foot syndrome (from 41% to 53%) (S; weak asso-	
		ciation: false discovery rate < 0.3)	
		The sensitivity of 496A>G for predicting grade II-III hand-foot	
		syndrome was 22% and the specificity 85%.	
		- No significant increase in the percentage of patients with	
		grade III-IV toxicity (NS).	
		- No significant increase in dose decreases (NS)	
		- No difference in mortality or progression-free survival (NS)	
		*13:	
		- The percentage *1/*13 was 0% among 43 patients with	
		grade IV-V toxicity or two forms of grade III-V toxicity and	
		1% in 99 randomly selected patients (NS)	
		The outborn indicated that the lock of accessibling with words	
		The authors indicated that the lack of association with grade	
		In-IV toxicity for each of the investigated SINPS is likely caused	
		NOTE: No associations were found for gene variants */ (1601	
		(1001) $(1001)$ $($	
		with severe toxicity have never been found in studies concer	
		ning these gene variants	
ref. 23 – FU/CAP	3	68 patients with advanced colorectal cancer were given adju-	Authors' conclusion:
mono/comb		vant or palliative treatment with fluoropyrimidine-based thera-	"Patients with the
Kristensen MH et		py. Therapy consisted of either a fluorouracil bolus injection	genetic variant
al.		$500 \text{ mg/m}^2$ every 2 weeks plus folinic acid (n=24) or fluoroura-	IVS14+1 G/A or
Variants in the		cil (400 mg/m <sup>2</sup> bolus plus 600 mg/m <sup>2</sup> by infusion every 2	c1896 C/T in the
	I		1

dihydropyrimidine dehydrogenase, methylenetetra- hydrofolate reduc- tase and thymi- dylate synthase genes predict early toxicity of 5- fluorouracil in colorectal cancer patients. J Int Med Res 2010;38:870-83. PubMed PMID: 20819423. <b>ref. 23, continua- tion</b>	AS 1.5: E	<ul> <li>weeks) plus folinic acid and oxaliplatin (n=27) or capecitabine 1250 mg/m<sup>2</sup> twice daily for 14 days every 3 weeks (n=17). There was no significant difference between incidences of grade I-IV toxicity in the first 2 cycles caused by the different chemotherapies. However, the proportion of grade III-IV toxicity did differ (67%, 33% and 0% respectively).</li> <li>Results: <ul> <li>Higher frequency of 1896C&gt;T in the group with grade I-IV toxicity than in the group without toxicity (13% versus 2% 1896T heterozygotes; there were no homozygotes; RR = 6) (S)</li> <li>Of the 4 1896T heterozygotes, 2 developed grade III-IV toxicity; the number of patients with toxicity was 24, the number of patients with toxicity was 24, the number of patients without was 44.</li> <li>This is equivalent to 8.3% 1896T heterozygotes in the group with grade III-IV toxicity. This is equivalent to an RR of 1.8 for grade III-IV toxicity.</li> </ul> </li> </ul>	DPYD gene had a statistically signifi- cant increased risk of experiencing toxi- city (RR 2 and 6, respectively), both having a high speci- ficity (0.97 and 0.98, respectively) and low sensitivity (0.04 and 0.13, respecti- vely). It is concluded that pretreatment detection of genetic variants can help to predict early toxicity experienced by patients receiving 5- FU-based chemo- therapy."
ref. 24 – FU/CAP, comb Gross E et al. Strong associa- tion of a common dihydropyrimidine dehydrogenase gene polymor- phism with fluoro- pyrimidine-related toxicity in cancer patients. PLoS ONE 2008;3:e4003.	3 AS 1.5: F AS 1: E	<ul> <li>128 Caucasian patients including 39 with poor tolerance to FU combination therapy (grade III or IV toxicity). 2 of the patients with poor tolerance died as a result of FU-associated toxicity. Independent group of 53 patients with poor tolerance to FU (n=39) or capecitabine combination therapy (n=14). The presence of variants was investigated by fully sequencing the DPD alleles.</li> <li>Variant 496A&gt;G: <ul> <li>Strongest association with grade III and IV toxicity: OR = 4.42 [95% CI = 2.12-9.23] for 92 patients with toxicity.</li> <li>The polymorphism attributable risk was 56.9%.</li> <li>The association was significant in patients with breast and gastro-oesophageal cancer (n=56 and n=158), but was non-significant in colon cancer patients n=128).</li> <li>I of the fatalities was heterozygous.</li> <li>All 3 homozygotes had grade III or IV toxicity.</li> </ul> </li> <li>Grade III and IV toxicity (especially diarrhoea and handfoot syndrome) also occurred in carriers using capecitabine-based chemotherapy. Chemotherapy was discontinued in 2 of these.</li> <li>The association was significant in patients with breast and gastro-oesophageal cancer (n=46 and n=146), but was non-significant in colon cancer patients using capecitabine-based chemotherapy.</li> </ul> <li>Variant IVS10-15T&gt;C: <ul> <li>Association with grade III and IV toxicity.</li> <li>The association was significant in patients with breast and gastro-oesophageal cancer (n=46 and n=146), but was non-significant in colon cancer patients (n=58).</li> </ul> </li> <li>Variant *2A (IVS14+1G&gt;A): <ul> <li>Low allele frequency in these groups (0.03 in patients with severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and patients without severe toxicity; 0 in healthy people and pati</li></ul></li>	Authors' conclusion: "Our results show compelling evidence that, at least in distinct tumor types, a common DPYD polymorphism strongly contributes to the occurrence of fluoropyrimidine- related drug adverse events. Carriers of this variant could benefit from indivi- dual dose adjust- ment of the fluoro- pyrimidine drug or alternate therapies."
ref. 25 – FU,	3	76 French patients with advanced colon cancer received	Authors' conclusion:
<b>mono</b> Capitain O et al. The influence of		weekly or two-weekly FU plus folinic acid (initial FU dose 1200 and 2500 mg/m <sup>2</sup> respectively; by continuous infusion, 2-weekly regimen partially using a bolus (400 mg/m <sup>2</sup> ); dose adjust-	"Toxicity was linked to low UH2/U ratio, 2846 A>T, IVS14+1

fluorouracil out- come parameters on tolerance and efficacy in pa- tients with advan- ced colorectal cancer. Pharmacogeno- mics J 2008;8:256-67. <b>ref. 25, continua-</b> <b>tion</b>	AS 1-1.5: E (2)#	<ul> <li>ments based on a target AUC of 25 mg.h/L; dose reduction of 10% in the event of significant grade II toxicity, discontinuation and dose decrease of 25% in the event of grade III toxicity and discontinuation of therapy in the event of grade IV toxicity), screening for *2A (IVS14+1G&gt;A), 2846A&gt;T, *13 (1679 T&gt;G) and 464T&gt;A and for DPD-deficient patients and also for 19 other variants.</li> <li>11.8% of the patients (n=9) displayed abnormally low clearance of FU associated with abnormal dihydrouracil/uracil plasma ratio prior to therapy. An SNP was found in 3 of these (2x 2846A&gt;T, 1x *2A).</li> <li>Despite pharmacological dose adjustments, the incidence of grade III and IV toxicity was higher in the group with reduced DPD activity (n=9) than in the group with normal DPD activity (33.3% versus 7.5%; S by 347%; OR = 6.20 [95% CI = 1.18-32.56]).</li> <li>The incidence of grade III and IV toxicity was higher in the group with SNPs (n=3) than in the group without SNPs (66.7% versus 8.2%; S by 711%).</li> <li>The authors indicated that the increased toxicity in DPD-deficient patients may have been prevented by reduced initial doses followed by pharmacokinetic dose adjustments.</li> </ul>	G>A for DPD."
<b>ref. 26 – FU</b> Sulzyc-Bielicka V et al. 5-Fluorouracil toxicity-attributa- ble IVS14 + 1G > A mutation of the dihydropyrimidine dehydrogenase gene in Polish colorectal cancer patients. Pharmacol Rep 2008;60:238-42.	3 AS 1: E (2) <sup>#</sup>	<ul> <li>252 Polish colon cancer patients received FU chemotherapy and screening for *2A (IVS14+1G&gt;A).</li> <li>1 patient was heterozygous. This patient was 1 of the 4 patients with grade III-IV neutropenia.</li> </ul>	Authors' conclusion: "We conclude that IVS14 + 1G > A DPYD (DPYD*2A) variant occurs in the Polish population and is responsible for a significant proportion of life- threatening toxicity of 5-FU."
ref. 27 – FU, mono Schwab M et al. Role of genetic and nongenetic factors for fluoro- uracil treatment- related severe toxicity: a pros- pective clinical trial by the German 5-FU Toxicity Study Group. J Clin Oncol 2008;26:2131-8.	3 AS 1: E	<ul> <li>683 German patients (670x *1/*1, 13x *1/*2A), of whom 110 with grade III/IV toxicity; FU monotherapy with folinic acid or levamisole; screening for *2A (IVS14+1G&gt;A) and also sequencing of exons and exon/intron transitions in 28 patients with grade IV toxicity, grade III toxicity or grade 0-II toxicity.</li> <li>*1/*2A versus *1/*1: <ul> <li>Increased risk of grade III/IV toxicity: OR = 4.67 [95% CI = 1.54-14.2] (S).</li> <li>Significantly increased risk of grade III/IV leukopenia and mucositis (OR = 10.19 [95% CI = 3.0-35.1] and OR = 5.8 [95% CI = 1.71-19.4] respectively), but not of grade III/IV diarrhoea.</li> <li>Significantly increased risk of grade III/IV toxicity in men (OR = 41.8 [95% CI = 9.2-190]), but not in women.</li> <li>The sensitivity of *2A genotyping for overall toxicity was 5.5% [95% CI = 0.02-0.11] with a positive predictive value of 0.46 [95% CI = 0.19-0.75].</li> </ul> </li> <li>Sequencing of 3x 28 patients with different toxicity classes: <ul> <li>12 additional SNPs, including 4 new ones.</li> <li>5 variants (623G&gt;A, *4 (1601G&gt;A), *6 (2194G&gt;A), 2846 A&gt;T and 2585G&gt;C) further investigated in ≥ 250 patients.</li> <li>2585G&gt;C was found in 1 patient with grade IV mucositis, but not in other patients (NS).</li> </ul> </li> </ul>	Authors' conclusion: "DPYD, TYMS, and MTHFR play a limi- ted role for FU rela- ted toxicity but a pronounced DPYD gene/sex-interaction increases prediction rate for male pa- tients."

ref. 27, continua- tion		<ul> <li>The percentage of patients with toxicity was increased for 2846A&gt;T (60% versus 16.1% in the overall population)</li> </ul>	
		<ul> <li>All other variants did not show a significant association with toxicity.</li> </ul>	
		<ul> <li>Inclusion of the additional variants only led to a marginal improvement in the prediction of overall toxicity.</li> </ul>	
		The method of administration is an independent risk factor: the risk of grade III/IV toxicity was greater for the bolus Mayo	
		regimen than for the high-dose infusion (OR=2.44 [95% Cl 1.52-3.91]).	
ref. 28 – FU,	3	59 French patients with inoperable head and neck cancer;	Authors' conclusion:
comb		determination of DPD activity (dihydrouracil/uracil ratio) prior	"5-FU dose tailoring
Mercier C et al.		to FU combination therapy or radio-chemotherapy; mild DPD	based upon DPD
prospective prie-		deficiency (dihydrouracil/uracil ratio < 0.5): FU dose was 80%	to 2 fold decrease in
for DPD deficien-		of the standard dose, severe DPD deficiency (ratio < $0.33$ ):	
cv prior to 5-FU		FU dose was 50% of the standard dose, complete DPD defi-	toxicities without
administration:			impairing efficacy."
city, not in effica-		- 25% of the patients had mild and 22% severe DPD deficien-	
J Clin Oncol		- 12% of the patients with DPD deficiency and dose reduction	
2008;26(May 20		showed severe toxicity. The incidence of severe toxicity was	
suppl):abstr		twofold lower in the overall group compared to the regimen	
14556.		There were no tovicity induced fotalities	
(meeting abstract)		- The effectiveness was similar to the regimen without dose	
		reduction (nercentages of responders 64% and 81% for first-	
		line chemotherapy and radio-chemotherapy and 50% and	
		38% for treatment for relapsed cancer).	
ref. 29 – FU,	3	<ul><li>38% for treatment for relapsed cancer).</li><li>50 American patients with locally advanced oesophageal</li></ul>	Authors' conclusion:
ref. 29 – FU, comb	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A,	Authors' conclusion: "Genotyping for
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al.	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received	Authors' conclusion: "Genotyping for polymorphisms
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo-	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura-	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo-	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase,
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi-	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and dutathiono S
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res-
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi-	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo-	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G>A), *5 (1627A>G), *6 (2194G>A) and *9A	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular	3	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G>A), *5 (1627A>G), *6 (2194G>A) and *9A (85T>C).	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate	3 AS 2 +	38% for treatment for relapsed cancer). 50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m <sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was tempo- rarily discontinued in the event of FU-related grade III-IV toxi- city, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G>A), *5 (1627A>G), *6 (2194G>A) and *9A (85T>C). - Almost all patients (94%) had at least 1 incident of grade III-	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate toxicity and pre-	3 AS 2 + AS 1: AA	<ul> <li>38% for treatment for relapsed cancer).</li> <li>50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m<sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was temporarily discontinued in the event of FU-related grade III-IV toxicity, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G&gt;A), *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C).</li> <li>Almost all patients (94%) had at least 1 incident of grade III-IV toxicity, including 3 fatalities.</li> </ul>	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
ref. 29 – FU, comb Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate toxicity and pre- dict outcomes:	3 AS 2 + AS 1: AA	<ul> <li>38% for treatment for relapsed cancer).</li> <li>50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m<sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was temporarily discontinued in the event of FU-related grade III-IV toxicity, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G&gt;A), *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C).</li> <li>Almost all patients (94%) had at least 1 incident of grade III-IV toxicity, including 3 fatalities.</li> <li>No significant associations of the polymorphisms with patho-</li> </ul>	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
ref. 29 – FU, comb Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate toxicity and pre- dict outcomes: North Central Cancer Treatment	3 AS 2 + AS 1: AA	<ul> <li>38% for treatment for relapsed cancer).</li> <li>50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m<sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was temporarily discontinued in the event of FU-related grade III-IV toxicity, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G&gt;A), *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C).</li> <li>Almost all patients (94%) had at least 1 incident of grade III-IV toxicity, including 3 fatalities.</li> <li>No significant associations of the polymorphisms with pathological complete response, time to progression/relapse of</li> </ul>	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
<b>ref. 29 – FU,</b> <b>comb</b> Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate toxicity and pre- dict outcomes: North Central Cancer Treatment Group (N0044).	3 AS 2 + AS 1: AA	<ul> <li>38% for treatment for relapsed cancer).</li> <li>50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m<sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was temporarily discontinued in the event of FU-related grade III-IV toxicity, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G&gt;A), *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C).</li> <li>Almost all patients (94%) had at least 1 incident of grade III-IV toxicity, including 3 fatalities.</li> <li>No significant associations of the polymorphisms with pathological complete response, time to progression/relapse of cancer, overall survival or grade III/IV toxicity.</li> </ul>	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
ref. 29 – FU, comb Jatoi A et al. Paclitaxel, carbo- platin, 5-fluoroura- cil, and radiation for locally advan- ced esophageal cancer: phase II results of prelimi- nary pharmacolo- gic and molecular efforts to mitigate toxicity and pre- dict outcomes: North Central Cancer Treatment Group (N0044). Am J Clin Oncol	3 AS 2 + AS 1: AA	<ul> <li>38% for treatment for relapsed cancer).</li> <li>50 American patients with locally advanced oesophageal cancer (11x *1/*1, 1x *1/*2A, 16x *1/*5, 3x *1/*6, 13x *1/*9A, 4x *9A/*9A, 1x *5/*5) participating in a phase II study received FU 225 mg/m<sup>2</sup> per day by continuous infusion in combination with carboplatin, paclitaxel and radiotherapy; FU was temporarily discontinued in the event of FU-related grade III-IV toxicity, after which the dose was decreased by 20%; patients received median 81% and 66% of the standard FU dose during 1 and 2 cycles respectively; screening for *2A (IVS14+1G&gt;A), *5 (1627A&gt;G), *6 (2194G&gt;A) and *9A (85T&gt;C).</li> <li>Almost all patients (94%) had at least 1 incident of grade III-IV toxicity, including 3 fatalities.</li> <li>No significant associations of the polymorphisms with pathological complete response, time to progression/relapse of cancer, overall survival or grade III/IV toxicity.</li> </ul>	Authors' conclusion: "Genotyping for polymorphisms of dihydropyrimidine dehydrogenase, cytochrome P3A4, and glutathione-S- transferase did not predict tumor res- ponse or serious adverse events."
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Di 5 Ciin i nanna-		was higher in the case group than in the control group (17%	
col		versus 2.7% and 6% versus 0% respectively).	
2007;64:237-40.		- Inverse association between lethal toxicity and DPD activity	
		(S).	
ref. 30, continua-		- Inverse association between the severity of the individual	
tion		types of toxicity (grade II central neurotoxicity; grade IV	
		mucositis, diarrhoea, neutropenia or thrombopenia) and	
		DPD activity (all five S). Median DPD activity was 1.6-3.2x	
		lower in patients with severe toxicity.	
		- Only 2 in 93 screened cases (2.2%) had ^2A (both ^1/^2A).	
	AS 1: E	Both had low DPD activity and high toxicity scores during the	
rof 21 EU/CAD	(2)"	1° cycle. Neither died.	Authors' conclusion:
mono	2	no thorapy (n=15) including 16 Caucasians 3 Afra Americana	"Screening natients
Saif MW et al		and 3 South Asians: screening for DPD activity in peripheral	for DPD deficiency
Dihvdropvrimidine		mononuclear blood cells and by genotyping	prior to administra-
dehydrogenase		mononuclear blood cens and by genotyping.	tion of 5-FU or cape-
deficiency (GPD)		- 30% of the patients had DPD deficiency (n=7) including 3	citabine using 2-13C
in GI malignan-		who were treated with FU (500 mg/m <sup>2</sup> per week or 425	uracil breath test
cies: experience		mg/m <sup>2</sup> per week) and folinic acid. 2 who were treated with	could potentially
of 4-years.		capecitabine 1800 mg/m <sup>2</sup> and 2 who were treated with high-	lower risk of toxici-
Pak J Med Sci Q		dose bolus FU (1400 mg/m <sup>2</sup> ) in combination with the uridine	ty."
2007;23:832-9.		prodrug 2',3',5'-tri-O-acetyluridine. The deficiency was confir-	
	AS 1: E	med by genotyping in 1 patient: he was *1/*2A.	
		- 28% of the DPD-deficient patients died due to toxicity (n=2),	
		including 1 to capecitabine and 1 to high-dose bolus FU.	
		- Rechallenge with capecitabine of a patient treated with FU/	
	_	folinic acid led to grade III hand-foot syndrome.	
ref. 32 – FU,	3	252 French patients with advanced colon cancer (163x *1/*1,	Authors' conclusion:
Mono Rejedren Celle M		6X ^1/28461, 1X ^9A/28461, 1X ^1/^2A, 1X -1590C/^2A, 1X	"Except in cases
DOISCION-CEILE IVI			
et al		(20,20,00,10,00,10,10,00,00,00,00,00,00,00,00	treatment is recom-
et al. 5-Eluorouracil-		*9A/*9A received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by	treatment is recom-
et al. 5-Fluorouracil- related severe		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens; plus folinic	treatment is recom- mended because the 5-FU metabo-
et al. 5-Fluorouracil- related severe toxicity: a compa-		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU	treatment is recom- mended because the 5-FU metabo- lism is close to zero,
et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion ( $C_{ss}$ );	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or
et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion ( $C_{ss}$ ); discontinuation of treatment in the event of grade IV toxicity;	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy-
et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion ( $C_{ss}$ ); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G>A), 2846A>T, *7 (295-	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict
et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy-		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (C <sub>ss</sub> ); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G>A), 2846A>T, *7 (295-298deITCAT), 1156G>T, *9A (85T>C), *9B (2657G>A), *10	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to
et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy- dropyrimidine debydrogenase		*9A/*9A) received either FU 400 mg/m <sup>2</sup> bolus + 2500 mg/m <sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m <sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion ( $C_{ss}$ ); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G>A), 2846A>T, *7 (295-298deITCAT), 1156G>T, *9A (85T>C), *9B (2657G>A), *10 (2983G>T), -1590T>C.	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to 5-FU treatment, pro- vided that the physi
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et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy- dropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.		<ul> <li>*9A/*9A) received either FU 400 mg/m<sup>2</sup> bolus + 2500 mg/m<sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m<sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (C<sub>ss</sub>); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G&gt;A), 2846A&gt;T, *7 (295-298deITCAT), 1156G&gt;T, *9A (85T&gt;C), *9B (2657G&gt;A), *10 (2983G&gt;T), -1590T&gt;C.</li> <li>(*1/*2A + -1590C/*2A) versus *1/*1:</li> <li>Clearance decreased by 80% (S; from 104.7 to 21.22 L/h per m<sup>2</sup>)</li> </ul>	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to 5-FU treatment, pro- vided that the physi- cian is aware of it and that added pre- cautions are taken,
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et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy- dropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.	AS 1: E AS 1.5: E	<ul> <li>*9A/*9A) received either FU 400 mg/m<sup>2</sup> bolus + 2500 mg/m<sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m<sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (C<sub>ss</sub>); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G&gt;A), 2846A&gt;T, *7 (295-298deITCAT), 1156G&gt;T, *9A (85T&gt;C), *9B (2657G&gt;A), *10 (2983G&gt;T), -1590T&gt;C.</li> <li>(*1/*2A + -1590C/*2A) versus *1/*1:</li> <li>Clearance decreased by 80% (S; from 104.7 to 21.22 L/h per m<sup>2</sup>)</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 793% (S; from 5.6% to 50.0%).</li> <li>(*1/2846T + 1x *9A/2846T) versus *1/*1:</li> <li>Clearance decreased by 40% and 58% for the two-weekly and weekly regimens respectively (both S; from 136.0 to 81.2 L/h per m<sup>2</sup> and from 104.7 to 43.9 L/h per m<sup>2</sup>).</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 1175% (S; from 5.6% to 71.4%).</li> </ul>	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to 5-FU treatment, pro- vided that the physi- cian is aware of it and that added pre- cautions are taken, such as an initial 5- FU dose reduction and an individual dose adjustment based on a close clinical and pharma- cokinetic follow-up." "In the case of a ho- mozygous status for
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et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy- dropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.	AS 1: E AS 1.5: E	<ul> <li>*9A/2040TH05C, 1X 1/2130C, 07X 1/3A, 1X 130C/3A, 10X</li> <li>*9A/*9A) received either FU 400 mg/m<sup>2</sup> bolus + 2500 mg/m<sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m<sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (Css); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G&gt;A), 2846A&gt;T, *7 (295-298deITCAT), 1156G&gt;T, *9A (85T&gt;C), *9B (2657G&gt;A), *10 (2983G&gt;T), -1590T&gt;C.</li> <li>(*1/*2A + -1590C/*2A) versus *1/*1:</li> <li>Clearance decreased by 80% (S; from 104.7 to 21.22 L/h per m<sup>2</sup>)</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 793% (S; from 5.6% to 50.0%).</li> <li>(*1/2846T + 1x *9A/2846T) versus *1/*1:</li> <li>Clearance decreased by 40% and 58% for the two-weekly and weekly regimens respectively (both S; from 136.0 to 81.2 L/h per m<sup>2</sup> and from 104.7 to 43.9 L/h per m<sup>2</sup>).</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 1175% (S; from 5.6% to 71.4%).</li> <li>*2A/2846T+85T versus *1/*1:</li> </ul>	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to 5-FU treatment, pro- vided that the physi- cian is aware of it and that added pre- cautions are taken, such as an initial 5- FU dose reduction and an individual dose adjustment based on a close clinical and pharma- cokinetic follow-up." "In the case of a ho- mozygous status for a relevant SNP, with a uracil plasma level
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et al. 5-Fluorouracil- related severe toxicity: a compa- rison of different methods for the pretherapeutic detection of dihy- dropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.	AS 1: E AS 1.5: E FENO: F (2) <sup>#</sup>	<ul> <li>*9A/*9A) received either FU 400 mg/m<sup>2</sup> bolus + 2500 mg/m<sup>2</sup> by 46-hour infusion every 2 weeks (n=168) or FU 1200 mg/m<sup>2</sup> by 4-hour infusion per week (n=84) (both regimens: plus folinic acid); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (Css); discontinuation of treatment in the event of grade IV toxicity; screening for *2A (IVS14+1G&gt;A), 2846A&gt;T, *7 (295-298deITCAT), 1156G&gt;T, *9A (85T&gt;C), *9B (2657G&gt;A), *10 (2983G&gt;T), -1590T&gt;C.</li> <li>(*1/*2A + -1590C/*2A) versus *1/*1:</li> <li>Clearance decreased by 80% (S; from 104.7 to 21.22 L/h per m<sup>2</sup>)</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 793% (S; from 5.6% to 50.0%).</li> <li>(*1/2846T + 1x *9A/2846T) versus *1/*1:</li> <li>Clearance decreased by 40% and 58% for the two-weekly and weekly regimens respectively (both S; from 136.0 to 81.2 L/h per m<sup>2</sup> and from 104.7 to 43.9 L/h per m<sup>2</sup>).</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 1175% (S; from 5.6% to 71.4%).</li> <li>*2A/2846T+85T versus *1/*1:</li> <li>Clearance decreased to almost 0 (NS; by almost 100%).</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 1686% (NS; from 5.6% to 100%).</li> <li>The patient had grade IV multi-organ toxicity and died after 40 days in Intensive Care.</li> <li>(1x *9A + 2x *9A) versus *1/*1:</li> </ul>	treatment is recom- mended because the 5-FU metabo- lism is close to zero, IVS14 + 1G>A or 2846A>T heterozy- gote are not strict contra-indications to 5-FU treatment, pro- vided that the physi- cian is aware of it and that added pre- cautions are taken, such as an initial 5- FU dose reduction and an individual dose adjustment based on a close clinical and pharma- cokinetic follow-up." "In the case of a ho- mozygous status for a relevant SNP, with a uracil plasma level higher than 100 lg/L or a UH2/U ratio be- low 1, then fluoropy- rimidine administra- tion must be discus- sed and an alterna-

rof 32 continua-		- No difference in clearance and incidence of toxicity (NS)	tive treatment pro-
tion			posed."
		- No difference in clearance and incidence of toxicity (NS).	Clearance versus
		Analysis of relevant SNPs had a high specificity (98.3%), but a low sensitivity (47.1%) for detecting DPD deficiency.	AS 2: AS 1.5: 55% AS 1: 20% FENO: almost 0%
ref. 33 – FU, mono Cho HJ et al. Thymidylate synthase (TYMS) and dihydropyri- midine dehydro- genase (DPYD) polymorphisms in the Korean popu- lation for predic- tion of 5-fluoro- uracil-associated toxicity. Ther Drug Monit	3 AS 1.5: AA AS 1: AA	<ul> <li>21 Korean colon cancer patients with grade III-IV toxicity on FU therapy (500 mg/m<sup>2</sup> by continuous infusion on days 1-5, plus folinic acid) and 100 healthy volunteers; screening by sequencing all exons and flanking introns.</li> <li>Very common variants (allele frequency 14-22%) in this Korean group were *5, 1737T&gt;C and 1896T&gt;C. No *2A was found.</li> <li>The percentage of patients without SNPs was similar to that in healthy volunteers (9.5% versus 10%).</li> <li>There was no significant correlation between specific genotypes and toxic response.</li> <li>NB: *5 does not have reduced DPD activity.</li> </ul>	Authors' conclusion: "The findings, from Korean patients with colon cancer, sug- gest that polymor- phisms of the DPYD gene are not asso- ciated with an in- creased risk for toxic response to 5-FU."
2007;29:190-6.			
ref. 34 – CAP, comb Salgado J et al. Polymorphisms in the thymidylate synthase and dihydropyrimidine dehydrogenase genes predict response and toxicity to capeci- tabine-raltitrexed in colorectal cancer. Oncol Rep 2007:17:225 8	3 AS 1: E (2) <sup>#</sup>	58 Spanish patients with advanced colon cancer received capecitabine (1000 mg/m <sup>2</sup> twice daily for 14 days) and raltitrexed every 3 weeks; screening for *2A (IVS14+1G>A). 1 patient was *1/*2A. This patient developed severe toxicity after the first cycle, after which FU was discontinued and more appropriate chemotherapy was started.	Authors' conclusion: "Considering the common use of fluoropyrimidines, genetic screening would be highly recommendable for the presence of the DPD gene mutation (IVS14+1G>A) rela- ted to toxicity, prior to 5-FU administra- tion."
ref. 35 – FU, comb Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucle- otide polymor- phisms on 5-fluo- rouracil tolerance. Mol Cancer Ther 2006;5:2895-904.	3 AS 0-1.5: E AS 1: F (2) <sup>#</sup> AS 0: E (2) <sup>#</sup>	<ul> <li>487 French patients (300x *1/*1, 10x *1/2846T, 8x *1/*2A, 1x - 1590C/*2A, 1x *2A/*2A, 6x *1/-1590C, 144x *1/*9A, 15x *9A/*9A, 1x *1/*13) received FU monotherapy (n=168) or one of 4 different FU combination therapies (n=319); dose adjustment from the second cycle based on the FU plasma concentration at the end of the previous infusion (Css); discontinuation of treatment or continuation with individual dose adjustment in the event of grade III/IV toxicity; screening for 22 relevant SNPs, including 9 in all patients *2A (IVS14+1G&gt;A), 2846A&gt;T, *7 (295-298deITCAT), 1156G&gt;T, *9A (85T&gt;C), *9B (2657G&gt;A), *10 (2983G&gt;T), -1590T&gt;C and *13 (1679T&gt;G)) in 171 patients with or without toxicity. 5 variants were found in the population.</li> <li>(*1/*2A + *2A/*2A + *1/2846T + *1/*13) versus *1/*1:</li> <li>Clearance decreased by 43% (S; from 132.3 to 74.9 L/h per m<sup>2</sup>)</li> <li>Increase in the percentage of patients with grade III-IV toxicity by 838% (S; from 6.6% to 61.9%).</li> <li>One *1/*2A patient died due to toxicity.</li> <li>The *2A/*2A patient developed grade IV diarrhoea, neutropenia and mucositis a few days after initiation of low-dose bolus FU in combination with epirubicin and cyclophospha-</li> </ul>	Authors' conclusion: "Pretreatment detec- tion of three DPYD SNPs could help to avoid serious toxic adverse events. This approach is suitable for clinical practice and should be compared or combined with pharmacologic approaches. In the case of dihydropyri- midine dehydroge- nase deficiency, 5- FU administration often can be safely continued with an individual dose adjustment."

tion       - Patients with SVPs: treatment was discontinued in 40% of AS 12: 55% AS 13: 55% AS 14: 55% does reduction and pharmacokinetic follow-up in the other 60%.       AS 15: 55% AS 1: 46% AS 1: 46% AS 1: 46%         (11/2A + 1/13) versus 1//1:       - Charance decreased by 54% (NS; from 132.5 to 60.8 L/h per m?)       AS 1.5: 55% AS 1: 46%         (11/2A + 1/13) versus 1//1:       - Charance decreased by 45% (NS; from 132.5 to 72.3 L/h per m?)       - Patients with evere brain the percentage of patients with grade III/V toxicity.         (11/2A + 1/159C) versus 1//1:       - No difference in the percentage of patients with grade III/V toxicity.       - No e of the homozygous patients had grade III/V toxicity.         The sensitivity and specificity of the analysis of the 3 most important SNPs for predicting toxicity were 0.31 and 0.88       Authors' conclusion: capecitabine monotherapy; screening for '2A (IVS14+IGsA).         LingTiller R et al.       AS 1: F       T3 Portuguese colon cancer patients (71x 1/r1, 1x 1/r2A, 1x as upper day identifies toxicity after treatment with capecitabine 1820 mg/m² per day SOP in exon 14: capecitabine reatment with capecitabine 1820 mg/m² per day SOP in exon 14: capecitabine reatment with grade III/IV toxicity, various FU we conclude that mutations in exon 14 for DPYD gene are reporting toxicity to 5-Fluorowardi.         Solze       73 Portuguese colon cancer patients (71x 1/r1, 1x 1/r2A, 1x A duttors' conclusion: '1/r3457), including 8 with grade III/IV toxicity, various FU we conclude that mutation in exon 14 correct patients, screening of the NS14 in 12/2A, 1x 2/r2A, 1x	ref. 35. continua-		mide. She was treated in Intensive Care for 15 days.	Clearance versus
the patients with severe toxicity and continued with a 25- 50% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- 50% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- 50% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- 50% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- solution and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- solution and pharmacokinetic follow-up in the other 60%.     AS 1.5: 55%       the patients with severe toxicity and continued with a 25- solution and pharmacokinetic follow-up in the other advanced breast cancer patients. Clin Cancer Res 2006; 12: 5496- 502.     The sensitivity and specificity of the analysis of the 3 most important SNPs for predicting toxicity were 0.31 and 0.98 respectively.     Authors' conclusion: "Our case report 1 patient was 11/2A. This patient died due to heamatological clargither treatment with capecitabine 1820 mg/m² per day of 12 days.     Authors' conclusion: "Our case report 1 patients. Clin Cancer Res 2006; 12: 5496- 502.     Authors' conclusion: "Unit 146 follydropyri- rindine dahydropyri- rindine dahydropyri- rindine dahydropyri- rindine dahydropyri- rindine dahydropyri- rindine dahydropyri- rindine dahydropyri- a dof the VS14 + 16 A follow advanced breases that reduced DPD activity (serves on 14: "174, 16x 11/2A, 1x 2A/2A) and 54 controls, including 35 administration t	tion		- Patients with SNPs: treatment was discontinued in 40% of	AS 2:
S0% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1: 46%       S1: E     50% dose reduction and pharmacokinetic follow-up in the other 60%.     AS 1: 46%       S1: E     Clearance decreased by 54% (NS; from 132.5 to 60.8 L/h per m <sup>2</sup> )     S1: E       S1: E     Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )     S1: E       S1: E     Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )     S1: E       S1: E     No difference in clearance (NS; increased by 3%). No difference in clearance (NS; increased by 72.4 (NS141 HCA2), No difference in clearance (NS; increased by 72.4 (NS141 HCA2), No difference in monobreary; screening for 2/2 A (NS141 HCA2), 100 French patients with advanced breast cancer received pharmacogene toxicity after treatment with capecitabine 1820 mg/m <sup>2</sup> per day for 12 days.     Authors' conclusion: 100 file-threase for 12 days.       S1: E     3     73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x Netations in exon 14 of dihydropyri- midine dehydrogra- genese and 5. 100 rotuguese colorectal cancer patients.     3     73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x Netations in exon 14 of dihydropyri- midine dehydrogra- mates fits the percentage of patients with grade III/V toxicity various FU Netations in exon 14 of dihydropyri- midine dehydrogra- nease gene of 0%.     Authors' conclusion: 10 file-threate- ning toxicity to 5- Filocouracii, and should therefore be excludee before its administration to cancer patients; screening for D			the patients with severe toxicity and continued with a 25-	AS 1.5: 55%
oner 6U%.     Oner 6U%.       (*1/2A + *1/*13) versus *1/*1: - Clearance decreased by 54% (NS; from 132.5 to 60.8 L/h per m <sup>2</sup> )       *1/2246T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )       *1/246T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )       *1/246T versus *1/*1: - No significant difference in clearance (NS, increased by 35%), - No significant difference in the percentage of patients with grade III-V toxicity (NS). - None of the homozygous patients had grade III/V toxicity. The sensitivity and specificity of the analysis of the 3 most important SNPs for predicting toxicity were 0.31 and 0.98 respectively.       ref. 36 - CAP, mono Largiller R et al. Pharmacogene tos of capecita- bine in advanced breast cancer patients. Clin Cancer Res 2006;12:5406- 502.     3 73 Portuguese colon cancer patients (71x *1/*1, 1x *1/2A, 1x *1/1485T), including 8 with grade III/V toxicity, various FU toxicity by 1076% (S; from 8.5% to 100%).     Authors' conclusion: *104 DPVD gene are responsible for a sociated toxicity were observed an ancer patients.       SNPs in exon 14 (n=2) versus no SNPs in exon 14: - Increase in the percentage of patients with grade III/V toxicity, various FU toxicity by 1076% (S; from 8.5% to 100%).     Authors' conclusion: *104 DPVD gene are responsible for a sociated toxicity in portuguese colorecial cancer patients.       G0 Dutch patients with grade III/V toxicity on FU therapy (43x *1/*1, 16x *1/*2A, 1x *2A*2A) and 54 controls, including 35 cancer patients; screening for DPD activity (< 70% of the average activity in controls).       *0% of the cases had reduced DPD activity (< 70% of the average activity in controls).       *0% of the cases had reduced DPD activity (< 70% o			50% dose reduction and pharmacokinetic follow-up in the	AS 1: 46%
ref. 36 - CAP, mono       3       (*1/*2A + *1/*13) versus *1/*1:       - Clearance decreased by 54% (NS; from 132.5 to 60.8 L/h per m²)         ref. 36 - CAP, mono       3       (*1/*9A + *9A**9A + *1/-1590C) versus *1/*1:       - No difference in clearance (NS; increased by 3%),       - No difference in clearance (NS; increased by 3%),         ref. 36 - CAP, mono       3       - No significant difference in the percentage of patients with important SNPs for predicting toxicity were 0.31 and 0.98       Authors' conclusion:         ref. 37 - FU, mono       AS 1: F       AS 1: F       - Pharmacogenetics:       Authors' conclusion:         (2)*       105 French patients with advanced breast cancer received patients.       Authors' conclusion:       - Our case report toxicity ware 0.31 and 0.98         ref. 37 - FU, mono       AS 1: F       As 1: F       - 11/463T), including 8 with grade III/IV toxicity, various FU       Authors' conclusion:         Sigueiro N et al. Mutations in exon flad of bhydropytimide dehydrogenations in exon flad of bhydropytimide dehydrogenations in exon flad of bhydropytimide dehydrogenations in exon flag       Sigueiro N et al. Significant proportion of flic-threatenation to cancer patients.       Authors' conclusion:         Yin Fortuguese colon cancer patients with grade III/IV toxicity, various FU       Nutations in exon flad of bhydropytimide dehydrogenations in exon flad.       Authors' conclusion:         Yin Portuguese colon cancer patients, increange of patients with grade III/IV toxicity, various FU       Nuthors'				
<ul> <li>Clearance decreased by 54% (NS; from 132.5 to 60.8 L/h per m<sup>2</sup>)</li> <li>Clearance decreased by 55% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>No significant difference in clearance (NS; increased by 3%).</li> <li>No significant difference in clearance (NS; increased by 3%).</li> <li>No significant difference in clearance (NS; increased by 3%).</li> <li>No significant difference in the percentage of patients with grade III/IV toxicity. The sensitivity and specificity of the analysis of the 3 most important SNPs for predicting toxicity ure 0.31 and 0.98</li> <li>ref. 36 - CAP, and the indiverse of capacital.</li> <li>associated toxicity after treatment with capecitabine 1820 mg/m<sup>2</sup> per day Deficiency as a source of if e-threase for 12 days.</li> <li>Toxicity after treatment with capecitabine 1820 mg/m<sup>2</sup> per day Deficiency as a source of if e-threase tening toxicity under capecitabine treatment.</li> <li>Toxicity after treatment with capecitabine 1820 mg/m<sup>2</sup> per day Deficiency as a source of if e-threase for 12 days.</li> <li>Toxicity after treatment with capecitabine 1820 mg/m<sup>2</sup> per day Deficiency as a source of if e-threase sequencing of exo 14.</li> <li>AS 1: E</li> <li>Therease in the percentage of patients with grade III/IV toxicity, various FU we conclude that mutations in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Increase in the percentage of patients with grade III/IV toxicity on FU therapy (43x *1/*1, fax *1/*2A, 1x *2A*2A) and 54 controls, including 35 cancer patients; screening for 72A.</li> <li>Stort Earls screening for DPD activity (&lt; 70% of the average activity in controls).</li> <li>Bow of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>Bow of th</li></ul>			(*1/*2A + *1/*13) versus *1/*1	
per m <sup>2</sup> )       *1/2846T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )         *1/2846T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )       *1/2846T versus *1/*1: - No difference in clearance (NS; increased by 3%). - No a difference in clearance (NS; increased by 3%). - No difference in clearance (NS; increase by 1548% from 0.91%       Authors' conclusion:         ref. 36 – CAP, mono Largilier R et al. Pharmacogene- bine in advanced breast cancer patients. Clin Cancer Res 2006;12:5496- 502.       3       105 French patients with advanced breast cancer received. To 12 days.       Authors' conclusion:         ref. 37 – FU, mono cagecitable treat- patients. Glin cancer patients. Glin cancer patients. Glin cancer patients.       3       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x *1/1845T), including 8 with grade III/IV toxicity; various FU regimens; sequencing of exon 14.       Authors' conclusion: *1/1845T), including 8 with grade III/IV toxicity; various FU regimens; sequencing of patients with grade III/IV toxicity; various FU regimens; sequencing of patients with grade III/IV toxicity; various FU regimens; sequencing of patients with grade III/IV toxicity; various FU regimens; sequencing of DPD activity (< 70% of the apatients, screening for DPD activity (< 70% of the average activity in corrols).       Authors' conclusion: *1/1/1, 18x *1/*2A, 1x *2A*2A) and 54 controls,			- Clearance decreased by 54% (NS: from 132.5 to 60.8 L/h	
<ul> <li>*1/2846T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>*1/2846T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>*1/2846T versus *1/*1: - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>*1/2846T versus *1/*1: - No significant difference in the percentage of patients with grade III/V toxicity (NS). - None of the homozygous patients had grade III/V toxicity.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SNPs for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>*105 French patients with advanced breast cancer received pharmacogene tics of capecita- bine in advanced breast cancer patients.</li> <li>*21 PU, data *1.*F (2)*</li> <li>*2006;12:5496- 502.</li> <li>*2006;12:5496- 502.</li> <li>*2006;12:5496- 502.</li> <li>*3 T3 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1X versus in the percentage of patients with grade III/V toxicity: various FU regimens; sequencing of exon 14.</li> <li>*1/1845T), including 8 with grade III/V toxicity: various FU regimens; sequencing of exon 14.</li> <li>*1/1845T), including 8 with grade III/V toxicity: various FU regimens; sequencing of exon 14.</li> <li>*1/1845T), including 8 with grade III/V toxicity: various FU regimens; sequencing of exon 14.</li> <li>*1/1845T), including 8 with grade III/V toxicity: various FU regimens; sequencing of exon 14.</li> <li>*1/1845T, including 8 with grade III/V toxicity on FU therapy (4X) van Kuilenburg AB et al.</li> <li>*1/19, *1/*2A, 1X *2A**2A) and 54 controls, including 35 cancer patients.</li> <li>*1/11, 16x *1/*2A, 11x *1/*2A, 11x *1/*2A with grade III/V toxicity in peripheral mononuclear blood cells and for *2A.</li> <li>*00 Tothe cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>*29% of the cases had reduced DPD activity (&lt; 70% of the average activ</li></ul>			per m <sup>2</sup> )	
**1/2846T versus *1/*1:       - Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m <sup>2</sup> )         **1/2846T versus *1/*1:       - Clearance (NS; increased by 3%).         - No difference in clearance (NS; increased by 3%).       - No difference in the percentage of patients with grade III/V toxicity.         ref. 36 - CAP, mono       3       105 French patients with advanced breast cancer received capecitable monotherapy; screening for "2A (IVS14+1G>A).       Authors' conclusion: "Our case report case report insignment with capecitable 1820 mg/m <sup>2</sup> per day for 12 days.         ref. 37 - FU, mono       S 1: F       104 for the tomozygous patients (71x *1/*1, 1x *1/*2A, 1x *1/*1445T), including 8 with grade III/IV toxicity: various FU       Authors' conclusion: "Our case report clienting toxicity under case cancer patients.         salgueiro N et al.       AS 1: F       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x *1/*1445T), including 8 with grade III/IV toxicity: various FU       Authors' conclusion: "We conclude that mutations in exon 14 of dihydropyrimidine dahydrop         14 of dihydropyrimidine day       AS 1: E       SNPs in exon 14 (n=2) versus no SNPs in exon 14: - Increase in the percentage of patients with grade III/IV toxicity on FU therapy (43x *1/*1, 16x *1/*2A, 11x *1/*2A, 12x *1/*1, 16x *1/*2A, 12x *1/*1,				
<ul> <li>Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>Clearance (Acceased by 45% (NS; from 132.5 to 72.3 L/h per m<sup>2</sup>)</li> <li>Paper m<sup>2</sup>)</li> <li>(11/59A + '9A/'9A + '1/-1590C) versus *1/'1:         <ul> <li>No difference in clearance (NS, increased by 3%).</li> <li>No significant difference in the percentage of patients with grade III/V toxicity (NS).</li> <li>None of the homozygous patients had grade III/V toxicity.</li> </ul> </li> <li>The sensitivity and specificity of the analysis of the 3 most important SNPs for precising for '2A (IVS14+1G&gt;A).</li> <li>1 patient was '1/'2A. This patient died due to haematological concerpatients of 12 days.</li> <li>Terf. 37 – FU, mono</li> <li>Salgueiro N et al.</li> <li>SNPs in exon 14, 11/1845T), including 8 with grade III/IV toxicity, various FU regimens; sequencing of exon 14.</li> <li>SNPs in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Increase in the percentage of patients with grade III/IV toxicity, on FU therapy (43X administration to cancer patients. Clor Cancer Res 2004;6:102-7.</li> <li>For 502</li> <li>Fef. 37 – FU, mono</li> <li>SNPs in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Increase in the percentage of patients with grade III/IV toxicity on FU therapy (43X administration to cancer patients. Clor Cancer Patients.</li> <li>SNPs in exon 14 (n=2) Versus no SNPs in exon 14:</li> <li>Increase in the percentage of DPD activity (&lt; 70% of the cases had reduced DPD activity (&lt; 70% of the cases that reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>29% of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>29% of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>29% of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>29% of the cases had reduced DPD ac</li></ul>			*1/2846T versus *1/*1:	
per m*)       (*1/*9A + *3A*9A + *1/-1590C) versus *1/*1: - No difference in clearance (NS, increased by 3%). - No significant difference in the percentage of patients with grade III-IV toxicity (NS). - None of the homozygous patients had grade III/IV toxicity.         ref. 36 – CAP, mono       3         AS 1: F       AS 1: F         Pharmacogene- tics of capecita- bine in advanced breast cancer patients.       AS 1: F         Clin Cancer Res 2006;12:5496- 502.       3         73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x Mutations in exon 14 of dihytopyri- midine dehytop- genase and 5- fluorourcal toxici- ty in Portuguese colorectal cancer patients.       3         76. 37 – FU, mono       3       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x *1/1845T), including 8 with grade III/IV toxicity, various FU toxicity by 1076% (S; from 8.5% to 100%).       Authors' conclusion: "We conclude that mignitistration to capecitabine treat- ment."         SNPE in exon 14 (n=2) versus no SNPs in exon 14: of 192 character patients, scale of DP activity in peripheral monouclear biodo cells and for *2A.       Authors' conclusion: "Ve conclude that ing toxicity to 5- Fluorouracil, and should therefore be excluded before its administration to cancer patients, scancer patients, screening for DPD activity in peripheral monouclear blood cells and for *2A.       Authors' conclusion: "Our study demon- strates that a DPD deministration to cancer patients, screening for the cases had 1 or 2" 2% alieles.         - 60% of the cases had 1 or 2" 2A alieles.       Stifterminant of the warage activity in controls). - 2%% of the cases had 1 or 2" 2A alieles.			- Clearance decreased by 45% (NS; from 132.5 to 72.3 L/h	
ref. 36 - CAP,       None of the homozygous patients had grade III/IV toxicity (NS),       None of the homozygous patients had grade III/IV toxicity.         ref. 36 - CAP,       105 French patients with advanced breast cancer received       Authors' conclusion:         regilier R et al.       AS 1: F       1 patient was "1/"2A. This patient died due to haematological toxicity after treatment with capecitabine 1820 mg/m² per day       Authors' conclusion:         ref. 37 - FU, mono       3       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x       Authors' conclusion:         ref. 37 - FU, mono       3       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x       Authors' conclusion:         reginations in exon mono       3       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x       Authors' conclusion:         reginations in exon mono       3       73 Portuguese colon cancer patients with grade III/IV toxicity; various FU       We conclude that mutations in exon 14 of DPYD gene are responsible for a significant proportioxicity by 1076% (S; from 8.5% to 100%).       Authors' conclusion:         ref. 39 - FU       3       60 Dutch patients with grade III/IV toxicity on FU therapy (43x *1/*1, 16x *1/*2A, 1x *2A/*2A) and 54 controls, including 35 cancer patients, screening for DPD activity in peripheral monouclear blood cells and for *2A.       60% of the cases had reduced DPD activity (< 70% of the may areage activity in controls).			per m²)	
<ul> <li>In Statistic Procession of the Procesof the Procession of the Procession of the Procesion of the Proc</li></ul>			(*1/*9A + *9A/*9A + *1/-1590C) versus *1/*1:	
<ul> <li>No significant difference in the percentage of patients with grade III/IV toxicity.</li> <li>No no of the homozygous patients had grade III/IV toxicity.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SNPe for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SNPe for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SNPe for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most capecitabine monotherapy; screening for "2A (IVS14+162-A).</li> <li>T patient was "1/2-A. This patient died due to haematological DPD deficiency as a source of life-threatenting toxicity under capecitabine in advanced breast cancer patients.</li> <li>Clin Cancer Res 2006;12:5496-5022.</li> <li>Tef. 37 - FU, mono</li> <li>Salgueiro N et al. Mutations in exon 14 (n=2) versus no SNPs in exon 14:         <ul> <li>1 ncrease in the percentage of patients with grade III/V toxicity; various FU source of life-threatening toxicity by 1076% (S; from 8.5% to 100%).</li> <li>SNPs in exon 14 (n=2) versus no SNPs in exon 14:</li></ul></li></ul>			- No difference in clearance (NS, increased by 3%).	
grade III-IV toxicity (NS).       - None of the homozygous patients had grade III/IV toxicity.         ref. 36 - CAP, mono       3         mono       AS 1: F         Pharmacogenetics of capecitable in advanced breast cancer received patients.       Authors' conclusion: "Our case report capecitable in advanced breast cancer received capecitable in advanced breast cancer patients.       Authors' conclusion: "Our case report capecitable in advanced breast cancer received capecitable in advanced breast cancer received patients.       Authors' conclusion: "Our case report capecitable in advanced breast cancer received capecitable frequency as a source of life-threastering toxicity under capecitable reat-ment."         2006;12:5496-502.       73 Portuguese colon cancer patients (71x *1/*1, 1x *1/*2A, 1x *1/*2			- No significant difference in the percentage of patients with	
<ul> <li>None of the homozygous patients had grade III/IV toxicity.</li> <li>None of the homozygous patients had grade III/IV toxicity.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SIPs for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SIPs for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SIPs for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>The sensitivity and specificity of the analysis of the 3 most important SIPs for predicting toxicity were 0.31 and 0.98 respectively.</li> <li>Taglilier R et al.</li> <li>AS 1: F</li> <li>(2)<sup>#</sup> toxicity after treatment with capecitabine monotherapy: screening for '2A (VS14+1G:A).</li> <li>Taptients as '1/'2A. This patient died due to haematological toxicity under treatment with capecitabine (VS14+1G:A).</li> <li>Taglilier R et al.</li> <li>Clin Cancer Res 2006;12:5496-502.</li> <li>Tef. 37 - FU, mono 14 (n=2) versus no SNPs in exon 14:</li> <li>Solves in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>NPs in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Solves in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Solves in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Solves in exon 14 (n=2) versus no SNPs in exon 14:</li> <li>Solve of the cases had reduced DPD activity (robe).</li> <li>Solve of the cases had reduced DPD activity in peripheral mononuclear blood cells and for "2A.</li> <li>Solve as had reduced DPD activity (&lt; 70% of the cases had reduced DPD activity (&lt; 70% of the taverage activity in controls).</li> <li>Solve as the ad of a '2A alleles.</li> <li>Significantly higher "2A allele frequency in the cases than in the general population (S; increase by 1548% from 0.91% to in Watalton in the dinydropyrimidas to in the dinydropyrimidas to i</li></ul>			grade III-IV toxicity (NS).	
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ty in Portuguese colorectal cancer patients. Genet Med 2004;6:102-7. <b>ref. 38 – FU</b> Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydropyrimi- dine dehydroge- nase gene of pa- tients with severe 5-fluorouracil. associated toxici- ty. High prevalence	fluorouracil toxici-			ning toxicity to 5-
colorectal cancer patients. Genet Med 2004;6:102-7.should therefore be excluded before its administration to cancer patients."ref. 38 - FU Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydrogyrimi- dine dehydroge- nase gene of pa- tients with severe 5-fluorouracil- associated toxici- ty.360 Dutch patients with grade III/IV toxicity on FU therapy (43x *1/*1, 16x *1/*2A, 1x *2A/*2A) and 54 controls, including 35 cancer patients; screening for DPD activity in peripheral mononuclear blood cells and for *2A.Authors' conclusion: "Our study demon- strates that a DPD deficiency is the major determinant of 5FU-associated toxi- city. The apparently high prevalence of the general population (S; increase by 1548% from 0.91% to 15%).Should therefore be excluded before its administration to cancer patients."KS 1 + AS 0: EAS 1 + AS 0: EAS 1 + AS 0: EAS 1 + AS 0: ESignificantly higher *2A allele frequency in the cases than in the general population (S; increase by 1548% from 0.91% to 15%).Significantly higher *2A allele frequency in the cases than in the general population (S; increase by 1548% from 0.91% to 15%).Significantly higher *2A allele frequency in the case than in the general population (S; increase by 1548% from 0.91% to 15%).Significantly higher *2A allele frequency in the case than in the general population in cancer patients	ty in Portuguese			Fluorouracil, and
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Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydropyrimi- dine dehydroge- nase gene of pa- tients with severe 5-fluorouracil- associated toxici- ty.	ref. 38 – FU	3	60 Dutch patients with grade III/IV toxicity on FU therapy (43x	Authors' conclusion:
AB et al.cancer patients; screening for DPD activity in peripheral mononuclear blood cells and for *2A.strates that a DPD deficiency is the major determinant of 5FU-associated toxi- city. The apparently high prevalence of the dihydropyrimi- dine dehydroge- nase gene of pa- tients with severe 5-fluorouracil- associated toxici- ty.cancer patients; screening for DPD activity in peripheral mononuclear blood cells and for *2A.strates that a DPD deficiency is the major determinant of 5FU-associated toxi- city. The apparently high prevalence of the IVS14 + 1G>A mutation warrants genetic screening for this mutation in cancer patients	Van Kuilenburg	-	*1/*1, 16x *1/*2A, 1x *2A/*2A) and 54 controls, including 35	"Our study demon-
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or the IVS14 + 1G>A mutation in the dihydropyrimi- dine dehydroge- nase gene of pa- tients with severe 5-fluorouracil- associated toxici- ty. Major determinant of 5FU-associated toxi- city. The apparently high prevalence of the general population (S; increase by 1548% from 0.91% to 15%). Major determinant of 5FU-associated toxi- city. The apparently high prevalence of the IVS14 + 1G>A mutation warrants genetic screening for this mutation in cancer patients	High prevalence		mononuclear blood cells and for *2A.	deficiency is the
<ul> <li>19-A mutation in the dihydropyrimi-dine dehydroge-nase gene of patients with severe 5-fluorouracil-associated toxicity.</li> <li>AS 1 + AS 0: E</li> <li>AS 1 + AS 0: E</li> <li>- 60% of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>- 29% of the cases had 1 or 2 *2A alleles.</li> <li>- Significantly higher *2A allele frequency in the cases than in the general population (S; increase by 1548% from 0.91% to 15%).</li> <li>- 5-fluorouracil-associated toxici-ty.</li> </ul>	of the IVS14 +			major determinant of
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<ul> <li>anse gene of pa- tients with severe 5-fluorouracil- associated toxici- ty.</li> <li>AS 1 + AS 0: E</li> <li>AS 0: E</li> <li>AS 1 + AS 0: E</li> <li>AS 0: E</li> <li>AS 1 + AS 0: E</li> <li>AS 0:</li></ul>	dine dehvdroge-		average activity in controls).	high prevalence of
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tics	rnarmacogene-			perore the admini-
2002;12:555-8.	2002;12:555-8.			

ref. 39 – FU, mono Raida M et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5'-splice donor site of intron 14 in patients with severe 5-fluoro- uracil (5-FU)- related toxicity compared with controls. Clin Cancer Res 2001;7:2832-9.	3 AS 1: F (2) <sup>#</sup> AS 0: F (2) <sup>#</sup>	<ul> <li>25 German patients (19x *1/*1, 5x *1/*2A, 1x *2A/*2A) with grade III/IV toxicity on FU monotherapy (n=20), FU chemoradiotherapy (n=2) or FU combination therapy (n=3) and 851 controls, including 800 cancer patients; screening for *2A.</li> <li>24% of the cases had 1 or 2 *2A alleles.</li> <li>Higher *2A allele frequency in the cases than in the controls (NS; increase by 2879% from 0.47% to 14%).</li> <li>The homozygous patient and two heterozygous patients died due to toxicity.</li> </ul>	Authors' conclusion: "Routine screening for the exon 14-skip- ping mutation and subsequent indivi- dual determination of the 5-FU pharma- cokinetics of hetero- zygous patients provides a concept of individualized therapy and allows the avoidance of undesired treatment toxicity."
ref. 40 – FU, comb Yamaguchi K et al. Germline muta- tion of dihydropy- rimidine dehydro- genese gene a- mong a Japanese population in rela- tion to toxicity to 5-fluorouracil. Jpn J Cancer Res 2001:92:337-42.	3 AS 2 + AS 1.5: AA	<ul> <li>69 Japanese patients (61x *1/*1, 4x *1/*9A; 1x *1/*5; 1x *1/74G, 1x *1/812delT, 1x *1/1714G); FU combination therapy or monotherapy (FU: either 800 mg/m<sup>2</sup> by 1-hour infusion or 500 mg/m<sup>2</sup> per day on days 1 and 5 by continuous infusion); screening by PCR and sequencing.</li> <li>The percentage of patients with grade III/IV toxicity was lower among the 8 heterozygous patients than among the *1/*1 patients (NS; decrease by 18% to 0%).</li> <li>NB: *5 and *9A do not have reduced DPD activity.</li> </ul>	Authors' conclusion: "Our observations of Japanese patients implied that the heterozygote is not associated with increased toxic response to 5FU."
ref. 41– FU van Kuilenburg AB et al. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5- fluorouracil- associated toxicity: identification of new mutations in the DPD gene. Clin Cancer Res 2000;6:4705-12.	3 AS 1-1.5: E	<ul> <li>37 Dutch patients with grade III/IV toxicity on FU therapy and 22 controls; sequencing of introns and intron-exon transitions.</li> <li>59% of the cases had reduced DPD activity (&lt; 70% of the average activity in controls).</li> <li>Weak but significant correlation between DPD activity and time to toxicity.</li> <li>Higher prevalence of grade IV neutropenia in patients with reduced DPD activity compared to those with normal DPD activity (S; increased by 323%, from 13% to 55%). No higher prevalence of other types of toxicity.</li> <li>79% of 14 patients with reduced DPD activity had 1 or 2 allele variants (3x *1/*1, 4x *1/*2A, 1x *2A/*9A, 1x *2A/*5, 1x *9A/496G, 1x *9A/496G/2846T, 1x *1/*5, 1x *5/*9A, 1x *6/*6).</li> <li>NB: *5, *6 and *9A do not have reduced DPD activity.</li> </ul>	Authors' conclusion: "Our results demon- strated that at least 57% (8 of 14) of the patients with a redu- ced DPD activity have a molecular basis for their defi- cient phenotype."
ref. 42 – FU, cutaneous Johnson MR et al. Life-threatening toxicity in a dihydropyrimidine dehydrogenase- deficient patient after treatment with topical 5- fluorouracil. Clin Cancer Res	2 AS 0: D	A 76-year-old white man developed severe stomatitis, severe inflammatory colitis, erythematous rash, neutropenia $0.6x10^9$ /L and thrombocytopenia $57x10^9$ /L one week after initiation of 5% FU cream twice daily on the scalp for the treatment of basal cell cancer. FU was discontinued and the patient made a gradual recovery over 3 weeks. The patient was *2A/*2A and had no detectable DPD enzyme activity in peripheral mononuclear blood cells. Assuming 10% cutaneous absorption, the authors estimate that application of 2 g of 5% FU cream leads to a total absorbed dose of ~20 mg/day (~0.33 mg/kg for this patient). This is much lower than the IV bolus FU dose of 500-550	Authors' conclusion: "This study repre- sents the first cha- racterization of a DPDdeficient patient who developed life- threatening toxicity after exposure to topical 5-FU. Consi- dering the previous- ly reported low cu- taneous absorption

1999;5:2006-11. ref. 42, continua- tion		mg/kg that is generally used for chemotherapy.	rate (~10%) of topi- cal 5-FU, we sug- gest that life-threate- ning toxicity in the population of pa- tients receiving topi- cal 5-FU will be limi- ted to profoundly DPD-deficient pa- tients (no measura- ble DPD enzyme activity)."
<b>ref. 43 – FU</b> SmPC Fluoroura- cil PCH 15-10-12.	0 AS 0-1.5 + FENO:	<u>Warning</u> : There have been reports of increased fluorouracil toxicity in patients with partially functional or non-functional dihydropyrimidine dehydrogenase (DPD). If appropriate, DPD enzyme activity should be determined prior to treatment with	
<b>ref. 44 – FU</b> SmPC Efudix (5- fluorouracil) cream 08-10-18.	0 AS 0-1.5 + FENO: E	<u>Warning</u> : Individuals with a defect in the enzyme dihydropyri- midine dehydrogenase (DPD) may be susceptible to severe systemic toxicity on use of standard doses of Efudix due to an increased systemic fluorouracil concentration. Evaluation of DPD activity may be considered in patients with confirmed or suspected systemic toxicity. Due to the relationship between DPD deficiency and systemic toxicity, individuals known to have DPD enzyme deficiency should be intensively monitored for systemic toxicity during Efudix treatment. <u>Adverse events</u> : Frequency not known: haematological condi- tions, such as pancytopenia, neutropenia, thrombocytopenia, leukocytosis; haemorrhagic diarrhoea, diarrhoea, vomiting, stomach pain, stomatitis, rash, nasal mucositis.* * Haematological conditions, stomatitis, rash, nasal mucositis (associated with systemic toxicity to medicinal products).	
ref. 45 - CAP SPC Xeloda (capecitabine) 20- 04-18.	0 AS 0: F AS 1-1.5 + FENO: E	<u>Contraindications</u> : Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. <u>Warning</u> : Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with Xeloda. No dose has been proven safe for patients with complete absence of DPD activity. Patients with certain heterozy-gous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have been shown to have increased risk of severe toxicity when treated with capecitabine. The frequency of the heterozygous DPYD*2A genotype in the DPYD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G. Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity. Data on the frequency of these DPYD variants in other populations than Caucasian is limited. It cannot be excluded	

ret. 45, continua-		that other rare variants may also be associated with an increa-	
tion		sed risk of severe toxicity.	
		For patients with partial DPD deficiency (such as those with	
		heterozygous mutations in the DPYD gene) and where the	
		benefits of Xeloda are considered to outweigh the risks (taking	
		into account the suitability of an alternative non-fluoropyrimi-	
		dine chemotherapeutic regimen), these patients must be trea-	
		ted with extreme caution and frequent monitoring with dose	
		adjusment according to toxicity. A reduction of the starting	
		dose in these patients may be considered to avoid serious	
		toxicity. There is insufficient data to recommend a specific	
		dose in patients with partial DPD activity as measured by	
		specific test. It has been reported that the DPYD*2A, c.1679	
		T>G variants lead to a greater reduction in enzymatic activity	
		than the other variants with a higher risk of side effects. The	
		consequences of a reduced dose for efficacy are currently	
		uncertain Therefore in the absence of serious toxicity the	
		dose could be increased while carefully monitoring the natient	
		The patients who are tested negative for the above-mentioned	
		alleles may still have a risk of severe adverse events. In	
		nations with unrecognised DPD deficiency treated with cape	
		eitabine as well as in these patients who test negative for	
		anagifia DDVD variational life threatoning toxicities manifesting	
		specific DFFD variations, me-timeatening toxicities mannesting	
		as acute overdose may occur. In the event of grade 2-4 acute	
		toxicity, treatment must be discontinued immediately. Perma-	
		nent discontinuation should be considered based on clinical	
		assessment of the onset, duration and severity of the obser-	
		Ved toxicities.	
ref. 46 – FU	0	Warning:	
SPC Fluorouracii		Based on postmarketing reports, patients with certain homo-	
29-07-16 (USA)		zygous or certain compound heterozygous mutations in the	
and other		DPD gene that result in complete or near complete absence of	
		DPD activity are at increased risk for acute early-onset of toxi-	
	AS 0: F	city and severe, life-threatening, or fatal adverse reactions	
		caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia,	
	AS 1-1.5	and neurotoxicity). Patients with partial DPD activity may also	
	+ FENO:	have increased risk of severe, life-threatening, or fatal adverse	
	F	reactions caused by fluorouracil.	
		Withhold or permanently discontinue fluorouracil based on	
		clinical assessment of the onset, duration and severity of the	
		observed toxicities in patients with evidence of acute early-	
		onset or unusually severe toxicity, which may indicate near	
		complete or total absence of DPD activity. No fluorouracil	
		dose has been proven safe for patients with complete absen-	
		ce of DPD activity. There is insufficient data to recommend a	
		specific dose in patients with partial DPD activity as measured	
		by any specific test.	
ref. 47 – FU	0	Contraindications: Carac should not be used in patients with	
SmPC Carac (5-		dihydropyrimidine dehydrogenase (DPD) deficiency. DPD	
tluorouracil)		deficiency may lead to fluorouracil entering the anabolic route,	
cream 16-12-03		resulting in cytotoxic activity and possible toxicity.	
(USA).		Warning: Patients should discontinue treatment with Carac if	
		symptoms of DPD deficiency develop.	
		Rare, unexpected systemic toxicity (e.g. stomatitis, diarrhoea,	
		neutropenia and neurotoxicity) associated with parenteral	
		administration of fluorouracil has been attributed to DPD	
		deficiency. A case of life-threatening systemic toxicity has	
	AS 0: E	been reported following topical use of 5% fluorouracil by a	
		patient with fully non-functional DPD. Symptoms included	
		patient with fully non-functional DPD. Symptoms included severe abdominal pain, haemorrhagic diarrhoea, vomiting.	
		patient with fully non-functional DPD. Symptoms included severe abdominal pain, haemorrhagic diarrhoea, vomiting, fever and chills. Physical examination showed stomatitis,	

ref. 47, continua-	<b>. 47, continua-</b> erythematous rash, neutropenia, thrombocytopenia,				
tion	ion inflammation of the oesophagus, stomach and small intestine.				
	Although this patient had used 5% fluorouracil cream, it is not				
	known whether patients with severe DPD deficiency develop				
	systemic toxicity in response to lower concentrations of				
	topically administered fluorouracil.				

<sup>#</sup> For studies that did not show significant differences for IM or PM due to very low numbers of IM or PM in the study (< 4), the effect for IM or PM was scored as if this concerned a case. This was indicated by placing the case code (2) behind the score.

<sup>1</sup>: SmPC Xeloda (capecitabine) 14-12-16 (USA).

Dialeman	AC 1.1 E and EENO with DDD inhibitane (unacil analague antivinal druga)
RISK Group	AS 1-1.5 and FENO with DPD inhibitors (uracil analogue antiviral grugs)

# Comments:

- Cases about systemic fluorouracil or capecitabine therapy were not included in the status report due to the large number of articles available. Kinetic studies from 2009 were only included if the kinetic parameters were given per genotype group. Clinical studies were only included if the patient numbers exceeded 500 (from 2009) or 1000 (from May 2014) and the patient numbers with partially functional activity were at least ten or if the study investigated a variant for which no studies were as yet included or if the study investigated the effect of dose adjustment. From 2009, articles investigating the effect of a group containing both polymorphisms known to increase the risk of toxicity and polymorphisms not known to increase the risk of toxicity were not included. If more than one article described data of the same patient group and the same polymorphisms, only the article with data from the largest amount of patients was included.
- Existing guidelines:
  - Amstutz U et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther 2018;103: 210-6. PubMed PMID: 29152729.

The authors consider \*2A, \*13, 1236G>A and 2846A>T to be of primary relevance due to their population frequency and established impact on enzyme function and toxicity risk. They indicate that \*2A and \*13 have the most deleterious impact on DPD activity, whereas 1236G>A and 2846A>T result in moderately reduced DPD activity. In addition, they indicate that 557A>G is a relatively common (3-5% carrier frequency) decreased function variant in individuals with African ancestry. However, in a supplementary table they indicate the evidence for an association of 557A>G with toxicity to be weak and for an association with DPD activity to be moderate. Based on current knowledge, they consider e.g. \*5, \*6 and \*9A to be fully functional. Dose recommendations are only available for \*2A, \*13, 1236G>A and 2846A>T. CPIC allocates a gene activity score of 0 to \*2A and \*13 and a gene activity score of 0.5 to 1236G>A and 2846A>T. In calculating the gene activity score of the genotype of a patient with two different decreased/no function variants, they presume these variants to be on different alleles. CPIC distinguishes the phenotypes intermediate metaboliser (including our phenotypes gene activity score 1.5, gene activity score 1, and the genotypes 1236A/ 1236A, 2846T/2846T and both 1236A and 2846T) and poor metabolisers (including gene activity score 0 and the genotypes \*2A plus 1236A, \*2A plus 2846T, \*13 plus 1236A, and \*13 plus 2846T). In the summary below, our phenotype nomenclature is used.

As evidence linking gene variants with 5-fluorouracil toxicity, CPIC mentions the meta-analysis of Meulendijks 2015. As evidence linking gene variants with DPD activity they mention the publications of Nie 2017 and of Offer 2013 (Nie Q et al. Quantitative contribution of rs75017182 to dihydropyrimidine dehydrogenase mRNA splicing and enzyme activity. Clin Pharmacol Ther 2017 [Epub ahead of print] and Offer SM et al. A DPYD variant (Y186C) in individuals of African ancestry is associated with reduced DPD enzyme activity. Clin Pharmacol Ther 2013;94:158-66). Nie 2017 indicates that the reduction in DPD activity is 50% and 68% in heterozygous carriers of \*2A and \*13, respectively. In addition, Nie 2017 indicates that the reduction in DPD activity is 30% and 35% in heterozygous carriers of 2846T and 1236A, respectively. In addition, Boisdron-Celle 2007 and Morel 2006 report a reduction in 5-fluorouracil clearance by 40-80% in heterozygous carriers of \*2A, 2846T and \*13. Offer 2013 indicates a 46% reduction in DPD activity in heterozygous carriers of 557A>G. In addition, CPIC indicates two publications measuring DPD activity after homozygous expression of gene variants *in vitro*.

The CPIC guideline is based on evidence from 91 included studies. Because we only included the most important clinical and *ex vivo* studies and no *in vitro* studies in our guideline, the number of included studies in our guideline is lower (32 up to March 2017).

CPIC indicates that the strength of the pharmacogenetic dosing recommendations is based on the known impact of some variants (\*2A, \*13, 2846T and 1236A) on DPD activity, the demonstrated relationship between DPD activity and 5-fluorouracil clearance, and between 5-fluorouracil exposure and its toxic effects. Patients who are heterozygous for decreased/no function variants demonstrate partial DPD deficien-

cy and should receive reduced starting doses. Based on Deenen 2016, CPIC concludes that a dose reduction of 50% is suitable for heterozygous carriers of no function variants. CPIC classifies this therapeutic recommendation as strong (i.e. "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects"). CPIC indicates that evidence is limited regarding the optimal degree of dose reduction for decreased function variants. Based on Deenen 2011 (average capecitabine dose reduction by 25% in \*1/2846T) and Lunenburg 2016 (safe treatment of 5 \*1/1236A with a 25% reduced capecitabine starting dose), CPIC concludes that heterozygous carriers of decreased function variants may tolerate higher doses compared to carriers of no function variants. CPIC indicates that in heterozygous carriers of a decreased function variant, the individual circumstances of a given patient should therefore be considered to determine if a more cautious approach (50% starting dose followed by dose titration), or an approach maximising potential effectiveness with a potentially higher toxicity risk (25% dose reduction) is preferable. CPIC classifies this therapeutic recommendation as moderate (i.e. "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects). Because some patients carrying decreased or no function variants tolerate normal doses of 5-fluorouracil

Because some patients carrying decreased or no function variants tolerate normal doses of 5-fluorouracil, CPIC indicates that to maintain effectiveness, doses should be increased in subsequent cycles in patients experiencing no or clinically tolerable toxicity in the first two chemotherapy cycles or with subtherapeutic plasma concentrations. Similarly, doses should be decreased in patients who do not tolerate the starting dose.

CPIC strongly recommends to avoid use of 5-fluorouracil-containing regimens in patients having two no function alleles or a no function allele and a decreased function allele. However, if no fluoropyrimidine-free regimens are considered a suitable therapeutic option, CPIC indicates that 5-fluorouracil administration at a strongly reduced dose combined with early therapeutic drug monitoring may be considered for patients with both a decreased function and a no function allele. However, CPIC notes that no reports of the successful administration of low-dose 5-fluorouracil in these patients were available at the time of guideline preparation. Assuming additive effects of decreased and no function alleles, it is estimated that a dose reduction of at least 75% would be required (i.e., starting dose < 25% of normal dose). CPIC indicates that in such cases a phenotyping test is advisable to estimate DPD activity and a starting dose. CPIC classifies this therapeutic recommendation as strong (i.e. "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects").

In an online November 2018 update, CPIC indicates the following:

The current guideline recommends to reduce the dose of fluoropyrimidines by 25-50% (from the full standard dose) in heterozygous carriers of decreased function variants. At the time of the guideline publication, this dose range was recommended due to limited evidence for genotype-guided dosing of decreased function alleles/variants. However, a recent prospective study (Henricks 2018 Lancet Oncol) provides evidence to support a recommendation for a 50% dose reduction in heterozygous carriers of the decreased function variants 2846A>T or 1236G>A. These data suggest that all Intermediate Metabolisers (gene activity score 1.5, gene activity score 1, and the genotypes 1236A/ 1236A, 2846T/2846T and both 1236A and 2846T) should receive a 50% dose reduction. Therefore CPIC revises its recommendation such that all Intermediate Metabolisers should receive a 50% dose reduction from the full standard starting dose, followed by dose titration based on clinical judgement and ideally therapeutic drug monitoring.

In addition, recent case reports from patients who are homozygous for 2846A>T indicate that a dose reduction of more than 50% may be required in some carriers of this genotype. Therefore, in patients with a 2846T/2846T genotype, clinicians should be aware that a > 50% reduction in starting dose might be warranted.

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Recommended dosing of illuorouracii of capecilabine by DPD phenotype					
Phenotype/	Therapeutic recommendation	Classification of recommendation			
genetypee					
AS 1.5	Reduce starting dose by 25 to 50% followed by titration of dose	Moderate			
	based on toxicity <sup>a</sup> or therapeutic drug monitoring (if available).				
	Online November 2018 update:				
	Reduce starting dose by 50% followed by titration of dose based on				
	toxicity <sup>a</sup> or therapeutic drug monitoring (if available).				
AS 1	Reduce starting dose by 50% followed by titration of dose based on	Strong			
	toxicity <sup>a</sup> or therapeutic drug monitoring (if available).				
1236A/1236A,	Reduce starting dose by 50% followed by titration of dose based on	Strong			
2846T/2846T,	toxicity <sup>a</sup> or therapeutic drug monitoring (if available).				
or 1236A plus	Online November 2018 update:				
2846T	Reduce starting dose by 50% followed by titration of dose based on				
	toxicity <sup>a</sup> or therapeutic drug monitoring (if available).				
	In patients with a 2846T/2846T genotype, clinicians should be aware				
	that a > 50% reduction in starting dose might be warranted.				

The therapeutic recommendations are indicated below:

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*2A plus	Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong
1236A, *2A	In the event, based on clinical advice, alternative agents are not	
plus 2846T,	considered a suitable therapeutic option, 5-fluorouracil should be	
*13 plus	administered at a strongly reduced dose <sup>b</sup> with early therapeutic drug	
1236A, or *13	monitoring. <sup>c</sup>	
plus 2846T		
ASO	Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens	Strong

AS 0 Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. Strong
 a: Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.

<sup>b</sup>: If available, a phenotyping test should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of < 25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance.</li>

<sup>c</sup>: Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

CPIC also refers to other gene-based dosing recommendations, i.e. the 2011 publication of our dosing recommendations in Clinical Pharmacology and Therapeutics and the warning against use in patients with DPD deficiency in the SmPCs of 5-fluorouracil and capecitabine from the United States of America and Canada.

On 25-2-2019, there was an online November 2018 update of the guideline present on the PharmGKB- and on the CPIC-site, which is included in the summary above.

Thorn CF et al. PharmGKB summary: fluoropyrimidine pathways. Pharmacogenet Genomics 2011;21:237-42. PubMed PMID: 20601926.

The PharmGKB mentions four polymorphisms that are associated with toxicity (\*2A, 496A>G, \*5 and \*9A). However, the latter two have not been associated with toxicity in studies and/or with reduced clearance or activity. These are therefore fully functional alleles.

The PharmGKB writes that \*2A has the highest association with fluoropyrimidine toxicity, although the frequency of this variant is less than 1% in Caucasians. However, the \*2A allele does not always correlate with reduced DPD activity *in vivo*. A recent study showed that \*2A has limited predictive capacity for severe fluorouracil toxicity. This capacity was more pronounced in male patients and with certain treatment protocols.

The PharmGKB concluded that the effect of DPYD on toxicity is clear. Given the low frequency of the variants, the unclear relationship between genotype and phenotype and the lack of diagnostic tests available before administration, the PharmGKB currently considers the effect not to be clinically relevant. More prospective studies are needed to investigate the influence of gender, treatment protocol, and additional unidentified DPYD variants on DPD-related toxicity.

- A cura del Gruppo di Lavoro di AIOM-SIF. Raccomandazioni per analisi farmacogenetiche. This unpublished Italian guideline is consulted for the UPGx project in 2016. For heterozygotes a dose reduction of 50% is recommended. In homozygotes the use of fluorouracil or capecitabine is contraindicated.
- Van Cutsem E et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
- According to this guideline, DPYD genotyping before starting fluoropyrimidine treatment is optional. <u>Positive and negative predictive values</u>:

In a study including 683 German patients (Schwab M et al., 2008), the positive predictive power of the \*2A allele for grade III/IV toxicity was 46% and the negative predictive power 85%. Of the patients with grade III/IV toxicity among this population, 5.5% had a \*2A allele compared to 29% in the Dutch population (Van Kuilenburg AB et al., 2002). This suggests that the \*2A allele has more significance in a Dutch population than in a German population.

In a study with 1606 \*2A-negative Dutch patients receiving therapy with capecitabine (90% of patients) or 5fluorouracil (10% of patients), either as combined chemotherapy (different combinations) or as monotherapy (with or without radiotherapy), the positive predictive value of 2846A>T, \*13 and 1236G>A combined for grade  $\geq$  3 toxicity in the first cycle was 13% and the negative predictive value 88% (Meulendijks 2017). In a study with 2594 patients from the USA treated with 12 cycles of adjuvant FOLFOX therapy (5-fluorouracil, folinic acid and oxaliplatin; 91.9% of patients) or FOLFIRI therapy (5-fluorouracil, folinic acid and irinotecan; 8.1% of patients) with or without cetuximab, the positive predictive value of the gene variants \*2A, \*13 and 2846A>T combined for 5-FU grade  $\geq$  3 toxicity was 81.8% and negative predictive value 68% (Lee 2014). The low negative predictive value might be attributed to the combination chemotherapy, which may add to the toxicities common to 5-fluorouracil.

In a meta-analysis of 8 cohort studies with in total 7365 patients, the positive predictive value of \*13 in prediction of grade  $\geq$  3 toxicity was 46% and the positive predictive value of 1236G>A 41% (Meulendijks 2015). Cost-effectiveness:

- Henricks LM et al. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Cancer 2019;107:60-7. PubMed PMID: 30544060. In patients treated with fluoropyrimidines in 17 Dutch hospitals (Henricks 2018 Lancet Oncol), genotypepatient and reduction of grade  $\geq$  3 toxicity in variant allele carriers). Variation of input data demonstrated that the screening strategy was very likely to be cost saving or worst case cost-neutral. Patients were screened for \*2A, \*13, 1236G>A and 2846A>T, followed by the use of 50% of the normal dose for \*1/\*2A and \*1/\*13 and 75% of the normal dose for \*1/1236A and \*1/2846T. Patients with more than 1 gene variant (homozy-gotes or compound heterozygotes) were individually treated and excluded from the study.

The calculation was from a health-care payer perspective. Only direct medical costs were included. The calculated costs of genotype-guided therapy were  $\in 2,599$  per patient and the calculated costs of not-geno-type-guided therapy  $\in 2,650$  per patient. The calculation was based on costs of hospitalisation in a nursing ward of  $\in 636$  per day, costs of hospitalisation in an intensive care unit of  $\in 2,015$  per day, additional costs for interventions related to toxicity (except hospitalisation) of  $\in 86$  for toxicity grade 0-2 and  $\in 234$  for toxicity grade  $\geq 3$ , costs of capecitabine tablets of  $\in 144.06$  per cycle, costs of 5-fluorouracil and administration at day care of  $\in 335.29$  per cycle, <u>cost of a medical doctor visit of  $\in 132$  per cycle</u>, a gene variant carrier frequency of 7.71%, and a genetic test price of  $\in 100$ . The risks of serious adverse events were derived from Henricks 2018 Lancet Oncol and other published studies.

Variation of input data ( $\pm$  20%) found genotype-guided therapy to have a high likelihood of being costsaving. It found average cost-savings of  $\in$  52 (95% interval range - $\in$  38 to  $\in$  176) per patient. Average gain in safety was 0.89% (95% interval range -0.04% to 1.79%). This gain in safety represents the difference between the proportion of patients treated without severe toxicity (both wild-type patients and gene variant carriers taken together) in the genotype-guided strategy and the non-genotype-guided strategy. The model was shown to be most sensitive to the frequency of the gene variants, followed by the risk of hospitalisation at the nursing ward for gene variant carriers receiving standard dose, and genotyping costs.

Cortejoso L et al. Cost-effectiveness of screening for DPYD polymorphisms to prevent neutropenia in cancer patients treated with fluoropyrimidines. Pharmacogenomics 2016;17:979-84. PubMed PMID: 27248859. The authors conclude that genotyping of \*2A, 2846A>T and \*13 using real-time PCR, TaqMan probes and a rapid cell lysis to provide PCR-ready DNA is cost effective in all fluoropyrimidine-based treatments. The costs for genotyping were € 6.40 per patient and the mean cost of treating severe neutropenia was € 3,044. Therefore, if severe fluoropyrimidine-induced neutropenia is reduced by genotyping the three DPYD variations in at least 2.21 cases per 1000 treated patients, DPYD genotyping will be cost effective.

The literature differs greatly with regard to the estimation of the percentage of adverse reactions that can be prevented by DPYD genotyping. A meta-analysis of \*2A and 2846A>T genotyping results estimated that each variant could identify 5% of patients with grade  $\geq$  3 adverse reactions to fluoropyrimidines with a specificity of 99%, independently of penetrance (Terrazino 2013). Therefore, a minimum 10% of adverse reactions could be avoided by genotyping both variants, since they are not in linkage disequilibrium. A review comparing capecitabine and 5-FU in monotherapy estimated the incidence of severe neutropenia to range from 2-2.6% (capecitabine) to 19.8-26% (5-FU) (Aguado C et al. Should capecitabine replace 5-fluorouracil in the first-line treatment of metastatic colorectal cancer? World J Gastroenterol 2014;20:6092-101). The frequency of severe neutropenia arising from fluoropyrimidine-based combination therapies has been reported to range between 5% (Skof E et al. Capecitabine plus irinotecan (XELIRI regimen) compared to 5-FU/LV plus irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective Phase II trial. BMC Cancer 2009;9:120) and 44% (Cassidy J et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011;105:58-64). The authors conclude that genotyping is likely to reduce neutropenia in more than 2.21 cases per 1000 treated patients (0.2% of patients).

The mean cost of treating 5-fluorouracil-induced severe neutropenia in 20 Spanish patients was  $\in$  3.044 (range  $\in$  17.45 to  $\in$ 14,103.25 per treatment). 45% of patients was treated with FOLFOX (5-FU plus oxaliplatin), 35% with FOLFOX plus monoclonal antibody, 15% with XELOX (capecitabine plus oxaliplatin) and 5% with FOLFIRI (5-FU plus irinotecan) plus monoclonal antibody. Neutropenia was grade 3 in 75% of patients and grade 4 (febrile neutropenia) in 25%.

The costs for genotyping 1000 patients in this Spanish centre (1000 genotyping samples per year (DPYD and other), 10 samples per run) were  $\in$  6,400 (range based on the number of samples per run and the number of samples analysed per year using the equipment:  $\in$  3.5 (2000 genotyping samples per year, 20 per run) to  $\in$  43.1 (100 genotyping samples per year, 1 per run)). Therefore, the range of neutropenia to be prevented is 1.15 to 14.16 cases per 1000 treated patients (0.1% to 1.4% of patients) for genotyping to be cost effective.

- Deenen MJ et al. Upfront genotyping of DPYD\*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016;34:227-34. PubMed PMID: 26573078.

In patients treated with fluoropyrimidines in three Dutch hospitals, \*2A-genotype-guided therapy was both cheaper and safer than not-genotype-guided therapy ( $\in$  45 reduced costs and reduction of grade  $\geq$  3 toxicity in \*2A-carriers with 62%). \*2A-genotype-guided therapy involved patients with genotype \*1/\*2A being started on  $\leq$  50% of the normal dose, followed by dose titration based on tolerance, and patients with genotype \*1/\*1 being started on the normal dose.

The calculation was from a health care payer perspective. Only direct medical costs were included. The calculated costs of genotype-guided therapy were € 2,772 per patient and the calculated costs of not-geno-type-guided therapy € 2,817 per patient. The calculation was based on costs of hospitalisation in a nursing

ward of  $\in$  497 per day, costs of hospitalisation in an intensive care unit of  $\in$  2,372 per day, additional costs for a medical intervention not requiring hospitalisation of  $\in$  50, costs of capecitabine tablets of  $\in$  292 per cycle, costs of 5-fluorouracil and administration at day care of  $\in$  401 per cycle, cost of a treating physician of  $\in$  78 per cycle, and a genetic test price of  $\in$  75. The risks of serious adverse events were derived from this study and other published studies.

Variation of input data ( $\pm$  20%) found \*2A-genotype-guided therapy to have a high likelihood of being costsaving. It found average cost savings of  $\in$  44 (range - $\in$  74 to  $\in$  331) per patient.

The model was shown to be most sensitive to the likelihood of toxicity-related hospitalisation of \*2A-carriers receiving the standard dose, followed by the \*2A-frequency, the genotyping costs and the duration of hospitalisation of \*2A-carriers receiving the standard dose.

Date of literature search: 30 January 2019.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics	AS 0	4F	Yes	Yes	13 May 2019
Working Group decision	FENO	4F	Yes	Yes	
	AS 1	4F	Yes	Yes	
	AS 1.5	4F	Yes	Yes	

#### Mechanism:

Fluorouracil is mainly (> 80%) converted by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites. Lower metabolic activity of DPD leads to increased intracellular concentrations of fluorodeoxyuridine monophosphate, the active metabolite of fluorouracil and its prodrug capecitabine. This leads to an increased risk of adverse events such as neutropenia, thrombopenia and hand-foot syndrome.

#### **Clinical Implication Score:**

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to genotype the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

# Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria		Given Score	
	Score	systemic	cutaneous
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-			
induced)	+		+
<ul> <li>CTCAE Grade 3 or 4 (clinical effect score D or E)</li> </ul>	++	++	
CTCAE Grade 5 (clinical effect score F)			
Level of evidence supporting the associated clinical effect grade ≥ 3			
<ul> <li>One study with level of evidence score ≥ 3</li> </ul>	+		
<ul> <li>Two studies with level of evidence score ≥ 3</li> </ul>	++		
<ul> <li>Three or more studies with level of evidence score ≥ 3</li> </ul>	+++	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical			
effect grade ≥ 3			
• 100 < NNG ≤ 1000	+	+	
• 10 < NNG ≤ 100	++		
<ul> <li>NNG ≤ 10</li> </ul>	+++		
PGx information in the Summary of Product Characteristics (SmPC)			
At least one genotype/phenotype mentioned	+		+
OR			
Recommendation to genotype	++	++	
OR			
At least one genotype/phenotype mentioned as a contra-indication in the	++		
corresponding section			

Total Score:	10+	8+	2+
Corresponding Clinical Implication Score:		Essential	Potentially beneficial