UGT1A1: irinotecan 1691 to 1694

*1/*28 = genotype leading to a reduced UGT1A1 activity, *28/*28 = genotype leading to a strongly reduced UGT1A1 activity, AUC = area under the concentration-time curve, CI = confidence interval, DPD = dihydropyrimidine dehydrogenase, 5-FU = 5-fluorouracil, HR = hazard ratio, HR_{adj} = adjusted hazard ratio, IM = IM, genotype otherwise = intermediate metaboliser, genotype otherwise = *1 in combination with an allele with reduced activity other than *28 (e.g. *1/*6), NS = non-significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, PM = PM, genotype otherwise = poor metaboliser, genotype otherwise = two alleles with reduced activity of which at least one other than *28 (e.g. *6/*28 or *6/*6), RR = relative risk, S = significant, SN-38 = active metabolite of irinotecan (7-ethyl-10-hydroxycamptothecin), SN-38G = 7-ethyl-10-hydroxy-camptothecin-glucuronide, UGT = uridine diphosphate glucuronosyltransferase UGT1A1*1 = TA_6 = [$A(TA)_6TAA$] = wild-type, UGT1A1*28 = TA_7 = [$A(TA)_7TAA$] (reduced UGT1A1 activity), UGT1A1*36 = TA_5 = [$A(TA)_5TAA$] (increased UGT1A1 activity), UGT1A1*37 = TA_8 = [$A(TA)_8TAA$] (UGT1A1 activity more strongly reduced than for *28), UGT1A1*6 = gene variant in Asians, reduced activity, comparable to *28.
grade 3/4 adverse event: see NCI-CTC table under 'comments' for more information.

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:
Irinotecan is a prodrug that is converted predominantly by carboxylesterases to the active metabolite SN-38, which has 100-1000-fold higher activity than irinotecan itself. Irinotecan is also metabolised by CYP3A4/5 to inactive metabolites. SN-38 is glucuronidated to the inactive metabolite SN-38-glucuronide by glucuronosyltransferases. SN-38 is predominantly metabolised by UGT1A1 and also by UGT1A6, UGT1A7, UGT1A9 and UGT1A10. Literature confirms an increase in SN-38 exposure for patients with a genetically reduced UGT1A1 activity (i.e. patients with one or more gene variants resulting in diminished UGT1A1 activity: *1/*28, IM genotype otherwise, *28/*28 or PM genotype otherwise) (Denlinger 2009, Minami 2007, Ramchandi 2007, De Jong 2006, Han 2006, Paoluzzi 2004, Innocenti 2004, Iyer 2002).
For *28/*28 and PM, there is ample evidence for an increased risk of serious adverse events at normal doses (also when compared to all other genotypes/phenotypes), while convincing evidence for an increased efficacy is lacking. Therefore, the KNMP Pharmacogenetics Working Group concludes that a gene-drug interaction is present and that it necessitates therapy adjustment (yes/yes-interactions).
For *1/*28 and IM, a similar amount of evidence is present. However, *1/*28 is the major group among Caucasian populations including the Dutch population. The standard irinotecan dose will therefore be based mainly on *1/*28. This is confirmed by Lu 2015 showing that most *1/*28+*1/*1 tolerate the standard dose and by the negligible dose adjustment calculated for *1/*28 compared to all genotypes (see below). This means that dose reduction for *1/*28 would lead in suboptimal doses for this patient group. Because the kinetic and clinical effects of *28 and *6 are comparable, the same is true for IM. Therefore, the KNMP Pharmacogenetics Working Group concludes that a gene-drug interaction is present, but that therapy adjustment is neither required nor advisable (yes/no-interactions).
Based on the above, the dose for *1/*1 may be increased. As three meta-analyses did not identify a difference in effectiveness of therapy between *1/*28 and *1/*1 (Dias 2014, Liu 2013, and Dias 2012), an increase for *1/*1 patients does not seem useful. Therefore, the KNMP Pharmacogenetics Working Group decided to refrain from a recommendation for *1/*1.
*Elaborate justification of choices and calculation of the dose adjustment for *28/*28 (and PM)*
There is strong evidence that the *28 and/or *6 variants are associated with an increased frequency of serious adverse events. All 9 meta-analyses investigating adverse events and 16 of the 23 studies found this increased risk (Yang 2018, Chen 2017, Liu 2017, Han 2014, Chen 2014, Liu 2014, Hu Clin Cancer Res 2010, Hu Eur J Cancer 2010, and Hoskins 2007; Tejpar 2018, Kweekel 2008, Liu 2008, Minami 2007, Côté 2007, Ramchandani 2007, de Jong 2006, Toffoli 2006, Han 2006, McLeod 2006, Massacesi 2006, Kitagawa 2005, Marcuello 2004, Rouits 2004, Innocenti 2004, and Ando 2000; Lankisch 2008, Stewart 2007, Zárate Romero 2006, Soepenberg 2005, Carlini 2005, Paoluzzi 2004, and Font 2003). In addition, all 7 meta-analyses and 3 studies investigating the effect of *28/*28 and/or *6/*6 and/or *6/*28 compared with all other genotypes, found that this risk was also increased for *28/*28 and/or PM patients compared to all other patients (Chen 2017, Liu 2017, Han 2014, Liu 2014, Hu Clin Cancer Res 2010, Hu Eur J Cancer 2010, Hoskins 2007; Tejpar 2018, Ramchandani 2007, Han 2006). Two of the three meta-analyses that

investigated grade 3-4 neutropenia showed that the risk of neutropenia was also elevated at low doses (Liu 2014 and Hu Clin Cancer Res 2010; Hoskins 2007). Two of the three meta-analyses that investigated grade 3-4 diarrhoea showed that the risk was elevated at high doses, but not at low doses (< 150 or 125 mg/m^2) (Liu 2014 and Hu Eur J Cancer 2010; Hoskins 2007). The meta-analysis of Hoskins 2007 also did not find an elevated diarrhoea risk at high doses. For *28, the meta-analysis of Yang 2018 found the risk of severe toxicity (including neutropenia and diarrhoea) to be elevated at high doses (> 150 mg/m^2), but not at low doses (< 150 mg/m^2). However, for *6 this meta-analysis found the risk to be increased at both high and low doses, with the ORs being higher at low doses. The most common doses used in the Netherlands are high doses (180 of 350 mg/m^2). Three of the five meta-analyses that investigated both neutropenia and diarrhoea showed that the risk of neutropenia increased more than the risk of diarrhoea (Yang 2018, Liu 2014, and Hoskins 2007; Chen 2017 and Liu 2017), but Yang 2018 showed this only for *28, not for *6. The fifth and second largest meta-analysis showed similar increased risk for diarrhoea and neutropenia for all patients, but in White patients only the risk for neutropenia was significantly increased (Liu 2017).

Four of the five meta-analyses and eight of the ten studies did not show the*28 and/or *6 variants to be associated with increased effectiveness of the treatment (Chen 2017, Dias 2014, Liu 2013, and Dias 2012; Liu 2017; Tejpar 2018; Kweekel 2008, Liu 2008, Côté 2007, Massacesi 2006, Carlini 2005, Marcuello 2004, and Font 2003; Toffoli 2006 and Han 2006). The fifth and largest meta-analysis (Liu 2017) found an increased efficacy for *1/*28+*28/*28 versus *1/*1. However, due to the *1/*28 and *28/*28 genotypes being analysed together, it is not clear whether this is also the case for *28/*28 separately. *1/*28 is the major group among White populations including the Dutch population. The standard irinotecan dose will therefore be based mainly on *1/*28. This is confirmed by Lu 2015 showing that most *1/*28+*1/*1 tolerate the standard dose, while most *28/*28 do not. Because development of severe adverse events results in temporary discontinuation of therapy, the effect of *28 on efficacy might be different in *1/*28 compared to *28/*28 (as suggested by Lu 2015). Moreover, the meta-analysis of Liu 2017 found the increased efficacy for *1/*28+ *28/*28 versus *1/*1 only in 4 retrospective studies with in total 538 patients and not in 12 prospective studies with in total 1292 patients, suggesting the significance of the result to be driven only by a small number of studies. Finally, the ORs for all patients and for all White patients in this meta-analysis were small (1.20 and 1.23). For these reasons, the KNMP Pharmacogenetics Working Group concludes that the evidence for an increased efficacy in *28/*28 and PM patients is not convincing enough to refrain from recommending a dose reduction in these patients.

The elevated frequency of serious adverse events in *28/*28 patients is consistent with the FDA advice in March 2005 (based on six studies) to add a passage to the Camptosar (irinotecan) SmPC that a reduction in the starting dose by at least one level of Camptosar should be considered for patients with the *28/*28 genotype.

All seven meta-analyses that investigated the effect of *1/*28 and/or *1/*6 found an elevated frequency of serious adverse events for *1/*28 and/or *1/*6 versus *1/*1 (Yang 2018, Chen 2017, Liu 2017, Chen 2014, Liu 2014, Hu Clin Cancer Res 2010, and Hu Eur J Cancer 2010). However, as indicated above, *1/*28 is the major group among White populations including the Dutch population. This group is larger than the *1/*1 group. The standard irinotecan dose will therefore be based mainly on *1/*28. This means that adjustment of the dose for this group is not useful or advisable.

Dose adjustments have been calculated on the basis of SN-38 AUC or clearance in studies:

*28/*28: The calculation was based on 6 studies with a total of 28 patients with *28/*28 (Goetz 2013, Denlinger 2009, De Jong 2006, Paoluzzi 2004, Innocenti 2004, and Iyer 2002). The weighted average of the calculated dose adjustment is a dose reduction to 58% (range 39%-85%, median 53%) of the dose for *1/*1 and to 69% (range 48%-92%, median 64%) of the dose for all patients. As the frequency of *1/*1 in Europe is less than 50%, and as caution should be exercised in reducing the dose, the calculated dose adjustment compared to all patients has been chosen. This was translated to 70% to be more achievable in clinical practice. Although the calculation leads to a broad range in outcomes and therefore does not strongly support a dose reduction, the eventual percentage is equivalent to the reduction used in practice if patients develop severe toxicity on irinotecan (20-30% reduction). In addition, Lu 2015 confirmed that the maximum dose tolerated by the largest group (40%) of *28/*28 patients was 33% lower than the normal dose, while the maximum dose tolerated by the largest group (40%) of *1/*1+*1/*28 patients was the normal dose. In this study, reduction of the initial dose with 33% for *28/*28 did not result in a toxicity and efficacy that were comparable to those for *1/*1+*1/*28 on normal dose. This might however be due to the subsequent dose escalation with maximum doses for *28/*28 being less than 33% lower compared to the maximum doses for *1/*1 and *1/*28.

PM: Because, the SN-38 glucuronide/SN-38 AUCs are almost the same for *28/*28 and *6/*6, suggestive of a similar effect on irinotecan metabolism (Minami 2007), the same dose reduction as for *28/*28 is recommended for PM, genotype otherwise.

*1/*28: A total of 112 patients with *1/*28 were present in the 6 studies used for dose calculation (Goetz 2013, Denlinger 2009, De Jong 2006, Paoluzzi 2004, Innocenti 2004, and Iyer 2002). The weighted average of the calculated dose adjustment is a dose reduction to 80% (range 63%-96%, median 79%) of the dose for *1/*1 and to 95% (range 79%-116%, median 98%) of the dose for all patients. As the frequency of *1/*1 in Europe is less than 50%, and as caution should be exercised in reducing the dose, the calculated dose adjustment compared to all patients has been chosen. This is equivalent to a dose reduction by 5% and is minor to the extent that it supports the choice not to advise therapy adjustment for *1/*28 (and IM) patients at this time.

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:
The KNMP Pharmacogenetics Working Group considers genotyping before starting irinotecan 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 UGT1A1 enzyme activity (*28/*28 and PM). This toxicity can be fatal (grade 5) (Rouits 2004). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug 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 14 studies and 9 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 ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
The number needed to genotype was deduced to be 41, using the data on Whites in the second largest meta-analysis (Liu 2017) and the prevalence of *28/*28 in the Dutch population. For White patients, Liu 2017 found only the risk for severe neutropenia to be increased for *28/*28 compared to *1/*1+*1/*28, not the risk for severe diarrhoea. In the 12 studies with Caucasian patients in this meta-analysis, the incidence of neutropenia grade 3-4 was 38% for *28/*28 and 11% for *1/*1+*1/*28. Thus, dose adjustment for *28/*28 leading to similar SN-38 concentrations as in *1/*1+*1/*28 on normal dose, would prevent neutropenia grade 3-4 in 27% of *28/*28. With a prevalence of *28/*28 in the Dutch population of 9%, this would amount to 2.4% of all Dutch patients, i.e. a number needed to genotype of 41.
The calculated number needed to genotype of 41 results in 2 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 ≥ 3 (2 points for 10 < NNG ≤ 100).
The Dutch Summary of Product Characteristics (SmPC) indicates that *28/*28 patients are at increased risk of haematological toxicity (grade 3 to 4) following administration of irinotecan at moderate or high doses (> 150 mg/m^2). 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 mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
In addition to the clinical implication score indicating pre-emptive genotyping to be essential, three of the four cost-effectiveness analyses suggest that pre-emptive genotyping followed by a 20%, 25%, or 50% dose reduction for *28/*28 or PM is cost saving and results in slightly more quality-adjusted life-years (Wei 2019, Gold 2009, and Obradovic 2008). The third cost-effectiveness analysis assumes the percentage of patients dying from irinotecan adverse events to be zero and suggests this strategy to be not cost-effective (additional costs of € 17,040,017 per quality adjusted life years gained) (Butzke 2016). Thus, three of the four cost-effectiveness analyses suggest that pre-emptive genotyping is not only essential, but also cost-saving. However, a systematic review of cost-effectiveness analyses concluded that current research does not support UGT1A1 polymorphism status as a cost-effective guide to irinotecan dosing (Henderson 2019). The latter is mainly based on the absence of firm evidence that genotype-based irinotecan dosing increases the number of QALY and the uncertainty whether the standard dose is optimal for wildtype and heterozygous patients. Recent studies suggest that irinotecan dose-escalation for wildtype and heterozygous patients might improve treatment outcome.

The table below follows KNMP nomenclature for UGT1A1 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Yang Y et al. UGT1A1*6 and UGT1A1*28 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479-e489.	3	Meta-analysis of 38 studies with a total of 6742 cancer patients treated with irinotecan, either as combined chemotherapy or as monotherapy. Irinotecan doses in the studies varied from 60 to 375 mg/m^2. 30 studies with a total of 3791 patients (2234x *1/*1, 1182x *1/*28, 275x *28/*28) investigated the effect of *28 on neutropenia. 25 studies with a total of 2780 patients (1568x *1/*1, 963x *1/*28, 249x *28/*28) investigated the effect of *28 on diarrhoea. All 34 studies could be used to investigate the effect of ethnicity, 30 studies to investigate the effect of irinotecan dose and 27 studies to investigate the effect of tumour type. 14 studies with a total of 2072 patients (1322x *1/*1, 606x	Authors' conclusion: 'Both UGT1A1*6 and UGT1A1*28 polymorphisms can be considered as predictors of irinotecan-induced toxicity, with effect varying by race, cancer type and irinotecan dose.'

PMID: 29932297.

ref. 1, continuation

*28/*28: E
*1/*28: E

*1/*6, 144x *6/*6) investigated the effect of *6 on neutropenia. 8 studies with a total of 900 patients (595x *1/*1, 249x *1/*6, 56x *6/*6) investigated the effect of *6 on diarrhoea. All 16 studies could be used to investigate the effect of ethnicity, 14 studies to investigate the effect of irinotecan dose and 11 studies to investigate the effect of tumour type. All studies investigating the effect of *6 were in Asians.
Of the 38 studies included in the meta-analysis, 7 were also included separately in this risk analysis (Kweekel 2008, Côté, 2007, Massacesi 2006, Toffoli 2006, Innocenti 2004, Rouits 2004, and Font 2003). A later publication of one study was also included in the meta-analysis (McLeod 2006).
Of the 38 studies in this meta-analysis, 23 were also included in the meta-analysis of Liu 2017, 12 in the meta-analysis of Liu 2014, 9 in the meta-analysis of Hu 2010 Eur J Cancer, 8 in the meta-analyses of Chen 2014 and Hu 2010 Clin Cancer Res, 7 in the meta-analysis of Han 2014, 4 in the meta-analysis of Hoskins 2007, and 2 in the meta-analysis of Chen 2017.
A random-effects model was used for the meta-analyses in case of significant heterogeneity. Otherwise, a fixed-effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
The authors indicate that the quality of eligible studies was evaluated by surveying the methodologies and trial design, but do not present quality scores for the included studies.
Publication bias was analysed, but only with Egger's test and the authors did not specify for which of the four meta-analyses (two outcomes (neutropenia and diarrhoea) and two comparisons (heterozygotes compared to no variant allele and homozygotes compared to no variant allele)) they investigated possible publication bias. No publication bias analyses were performed for the subgroups.

Results:

ORs (95% CI) for *1/*28 and *28/*28 versus *1/*1:

		*28/*28	*1/*28	incidence for *1/*1 (% of patients)
neutropenia grade III-IV		OR = 3.50 (2.23-5.50) (S)	OR = 1.91 (1.45-2.50) (S)	16%
diarrhoea grade III-IV		OR = 1.69 (1.20-2.40) (S)	OR = 1.45 (1.07-1.97) (S)	12%
severe toxicity	all ethnicities	OR = 2.28 (1.80-2.88) (S)	OR = 1.60 (1.30-1.97) (S)	
	Whites	OR = 2.43 (1.44-4.08) (S)	OR = 1.59 (1.17-2.17) (S)	
	Asians	OR = 2.94 (1.86-4.64) (S)	OR = 1.67 (1.29-2.17) (S)	
severe toxicity	all irinotecan doses	OR = 3.07 (2.09-4.52) (S)	OR = 1.77 (1.44-2.17) (S)	
	> 150 mg/m^2	OR = 3.48	OR = 1.81	

<table>
<tr><td>ref. 1, continuation</td><td>PM: E
IM: E</td><td>
<table>
<tr><td></td><td></td><td>(2.25-5.39) (S)</td><td>(1.46-2.25) (S)</td><td></td></tr>
<tr><td></td><td>< 150 mg/m^2</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>severe toxicity</td><td>all tumour types</td><td>OR = 2.76 (1.86-4.09) (S)</td><td>OR = 1.68 (1.37-2.06) (S)</td><td></td></tr>
<tr><td></td><td>digestive system</td><td>OR = 2.90 (1.95-4.30) (S)</td><td>OR = 1.73 (1.40-2.15) (S)</td><td></td></tr>
<tr><td></td><td>respiratory system</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td colspan="5">There was no statistically significant heterogeneity between the studies for the comparison of diarrhoea in *28/*28 versus *1/*1.
The heterogeneity between the studies was significant, but low, for the other comparisons.</td></tr>
<tr><td colspan="5">There was no publication bias according to the Egger’s test.</td></tr>
</table>
<table>
<tr><td colspan="5">ORs (95% CI) for *1/*6 and *6/*6 versus *1/*1:</td></tr>
<tr><td colspan="2"></td><td>*6/*6</td><td>*1/*6</td><td>incidence for *1/*1 (% of patients)</td></tr>
<tr><td colspan="2">neutropenia grade III-IV</td><td>OR = 3.03 (2.05-4.47) (S)</td><td>OR = 1.95 (1.34-2.85) (S)</td><td>17%</td></tr>
<tr><td colspan="2">diarrhoea grade III-IV</td><td>OR = 4.03 (1.98-8.32) (S)</td><td>OR = 1.98 (1.26-3.11) (S)</td><td>8.6%</td></tr>
<tr><td>severe toxicity</td><td>Asians (= the only ethnicity in the studies)</td><td>OR = 3.16 (2.25-4.44) (S)</td><td>OR = 1.95 (1.42-2.66) (S)</td><td></td></tr>
<tr><td>severe toxicity</td><td>all irinotecan doses</td><td>OR = 3.17 (2.24-4.48) (S)</td><td>OR = 2.08 (1.46-2.97) (S)</td><td></td></tr>
<tr><td></td><td>> 150 mg/m^2</td><td>OR = 2.91 (2.02-4.18) (S)</td><td>OR = 1.82 (1.28-2.57) (S)</td><td></td></tr>
<tr><td></td><td>< 150 mg/m^2</td><td>OR = 9.42 (2.43-36.5) (S)</td><td>OR = 3.49 (1.28-9.58) (S)</td><td></td></tr>
<tr><td>severe toxicity</td><td>all tumour types</td><td>OR = 3.21 (2.20-4.67) (S)</td><td>OR = 1.75 (1.22-2.52) (S)</td><td></td></tr>
<tr><td></td><td>digestive system</td><td>OR = 3.00 (2.04-4.42) (S)</td><td>OR = 1.66 (1.18-2.35) (S)</td><td></td></tr>
<tr><td></td><td>respiratory system (only 1 study)</td><td>OR = 18.2 (1.56-212) (S)</td><td>OR = 12.0 (1.02-141) (S)</td><td></td></tr>
<tr><td colspan="5">There was moderate heterogeneity between the studies for the comparison of neutropenia in *1/*6 versus *1/*1.
There was no statistically significant heterogeneity between the studies for the other comparisons.</td></tr>
<tr><td colspan="5">There was no publication bias according to the Egger’s test.</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 2
Tejpar S et al. Clinical and phar-</td><td>4</td><td colspan="2">574 colon cancer patients were treated with irinotecan 180 mg/m^2 every two weeks in combination with 5-fluorouracil and leucovorin for 6 months. Adverse events were assessed</td><td>Authors’ conclusion: ‘We found that a complex of risk</td></tr>
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<tr>
<td>macogenetic determinants of 5-fluorouracyl/ leucovorin/irinotecan toxicity: results of the PETACC-3 trial. Eur J Cancer. 2018;99:66-77. PMID: 29909091.

ref. 2, continuation</td>
<td>*28/*28: E</td>
<td>according to the National Cancer Institute Common Toxicity Criteria Grading System. Any grade III or IV toxic event resulted, as per protocol, in a 20% dose reduction for subsequent cycles after toxicity resolution or treatment was postponed. Periods with lowered chemotherapy doses were not included in the analysis of adverse events. Dose reduction was used as a global measure of toxicity.
69.6% of patients had stage III colon cancer.
28.2% of patients developed neutropenia grade III-IV, 9.0% neutropenia grade IV, 10.4% diarrhoea grade III-IV, and 21.2% a serious adverse event. A dose reduction was applied in 30.9% of patients.
Comedication other than hormone replacement therapy was not mentioned, but a strong effect of comedication on either UGT1A1 or severe adverse events is not expected.
In a parallel arm of this randomised clinical trial, 572 patients were treated with 5-fluorouracil and leucovorin for 6 months, allowing comparison of the effect of *28 in patients treated with and without irinotecan.
ORs were determined by multivariate regression analyses. Adjustment was for age, sex, body surface area-sex combination, WHO performance status, bilirubin > 0.5x the upper limit of normal, and in case of the neutropenia and dose reduction outcomes also for baseline neutrophils.

Genotyping (estimated based on the genotypes of the 568 patients included in the Kaplan-Meier curve):
- 234x *1/*1
- 258x *1/*28
- 82x *28/*28

Results:
<table>
<tr><td colspan="3">Results for *28/*28 compared to *1/*1+*1/*28 (neutropenia, and total serious adverse effects) or for *28/*28 versus *1/*28 versus *1/*1 (diarrhoea and dose reduction):</td></tr>
<tr><td></td><td></td><td>incidence for *1/*1+ *1/*28</td></tr>
<tr><td rowspan="4">neutropenia grade III-IV</td><td>OR_{adj} = 2.89 (1.65-5.07) (S)</td><td rowspan="4">28% of patients</td></tr>
<tr><td>Kaplan-Meier curve analysis showed *28/*28 to be associated with more frequent and earlier neutropenia grade III-IV (S).</td></tr>
<tr><td>In univariate analysis, there was no difference between *1/*1 and *1/*28.</td></tr>
<tr><td>The result was NS in the arm without irinotecan, confirming the result in the arm with irinotecan to be caused by the *28-irinotecan interaction.
The percentage of patients with neutropenia grade III-IV in the arm without irinotecan, was 23% of that in the arm with irinotecan (6.4% versus 28.2%).</td></tr>
<tr><td rowspan="2">neutropenia grade IV</td><td>OR_{adj} = 2.33 (1.03-5.24) (S)</td><td rowspan="2"></td></tr>
<tr><td>The result was NS in the arm without irinotecan,</td></tr>
</table>
</td>
<td>factors is involved in the development of toxicity, including UGT1A1. Parameters that are readily available in clinical practice, notably sex, age and performance status, are stronger predictors than the UGT1A1 *28 genotype.’</td>
</tr>
</table>

ref. 2, continuation	*1/*28: E		confirming the result in the arm with irinotecan to be caused by the *28-irinotecan interaction. The percentage of patients with neutropenia grade IV in the arm without irinotecan, was 28% of that in the arm with irinotecan (2.5% versus 9.0%).		
		diarrhoea grade III-IV	Trend for a decrease with increasing number of *28-alleles (p = 0.068) (NS).		
			A similar trend, albeit with a somewhat higher p-value (p = 0.136), was present in the arm without irinotecan, contradicting the result to be caused by the *28-irinotecan interaction. The percentage of patients with diarrhoea grade III-IV in the arm without irinotecan, was 49% of that in the arm with irinotecan (5.1% versus 10.4%).	
		total serious adverse events	x 1.7 (S)	0.40 per patient	
			The result was NS in the arm without irinotecan, confirming the result in the arm with irinotecan to be caused by the *28-irinotecan interaction. For *1/*1+*1/*28, the rate of serious adverse events in the arm without irinotecan, was 58% of the rate in the arm with irinotecan.		
		dose reduction	OR_{adj} per *28-allele = 1.35 (1.01-1.79) (S)		
			The result was NS in the arm without irinotecan, confirming the result in the arm with irinotecan to be caused by the *28-irinotecan interaction. The percentage of patients with dose reduction in the arm without irinotecan, was 50% of that in the arm with irinotecan (15.5% versus 30.9%).		
		relapse-free survival of stage III patients	*28/*28 showed a trend for a better survival in the arm with irinotecan than in the arm without irinotecan (p = 0.07) (NS), but *1/*1+*1/*28 did not.		
		Note: The gene variant 3156G>A was also determined. However, there was a strong association between *28 and 3156G>A and in bivariate logistic regression analysis with both gene variants, only *28 remained significant as predictor			

<table>
<tr><td>ref. 2, continuation</td><td></td><td>for bilirubin >0.5x upper limit of normal and as predictor for neutropenia grade III or grade IV. For this reason, no further analyses were performed for 3156G>A.</td><td></td></tr>
<tr><td>ref. 3
Chen X et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with lung cancer: a meta-analysis. Cancer Chemother Pharmacol 2017;79:1109-1117.
PubMed PMID: 28502040.

ref. 3, continuation</td><td>3</td><td>Meta-analysis of 9 studies with in total 577 Asian lung cancer patients treated with irinotecan, either as combined chemotherapy or as monotherapy. Irinotecan doses in the studies varied from 50 to 100 mg/m^2. In addition, the therapy interval is relatively long in lung cancer treatment.
Of the 9 studies included in the meta-analysis, 1 was also included separately in this risk analysis (Han 2006).
Of the 9 studies in this meta-analysis, 5 were also included in the meta-analysis of Liu 2017, 3 in the meta-analysis of Han 2014, 2 in the meta-analyses of Dias 2012 and Hu 2010 Eur J Cancer, and 1 in the meta-analysis of Chen 2014. None were included in the meta-analyses of Liu 2014 and Liu 2013 (both colorectal cancer and mainly Caucasian), Dias 2014, Hu 2010 Clin Cancer Res and Hoskins 2007.
Data on *28 were derived from 9 studies including a total of 524 patients. For diarrhoea, the comparison between *1/*28 and *1/*1 was based on 439 patients from 8 studies of which 78 *1/*28. The comparison between *28/*28 and *1/*1 was based on 104 patients from 3 studies of which 8 *28/*28. For neutropenia, the comparison between *1/*28 and *1/*1 was based on 412 patients from 7 studies of which 71 *1/*28. The comparison between *28/*28 and *1/*1 was based on 81 patients from 2 studies of which 5 *28/*28. For tumour response, the comparison between *1/*28+*28/*28 and *1/*1 was based on 316 patients from 7 studies of which 66 *1/*28+*28/*28.
Data on *6 were derived from 6 studies including a total of 441 patients. For diarrhoea, the comparison between *1/*6 and *1/*1 was based on 182 patients from 4 studies of which 61 *1/*6. The comparison between *6/*6 and *1/*1 was based on 80 patients from 3 studies of which 4 *6/*6. For neutropenia, the comparison between *1/*6 and *1/*1 was based on 153 patients from 3 studies of which 53 *1/*6. The comparison between *6/*6 and *1/*1 was based on 58 patients from 2 studies of which 3 *6/*6. For tumour response, the comparison between *1/*6+*6/*6 and *1/*1 was based on 182 patients from 4 studies of which 63 *1/*6+*6/*6.
Toxicity was defined as grade 3-4 toxicity and tumour response as the response rate.
A random-effects model was used for the meta-analysis in case of significant heterogeneity. Otherwise, a fixed-effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
The authors indicate that the quality of the included studies was evaluated based on information collected from the studies including study design, number of patients, population, mutation detection method, race, histology, Hardy-Weinberg equilibrium, chemotherapy regimen, grade criteria for neutropenia and diarrhoea and definitions of treatment outcome measures, but do not present quality scores for the studies.
Publication bias analysis was not performed.

Results:
ORs (95% CI) for *1/*28 and *28/*28 versus *1/*1:
<table><tr><td></td><td>*28/*28</td><td>*1/*28</td><td>incidence for *1/*1 (% of patients)</td></tr></table></td><td>Authors' conclusion: 'These data suggest that the UGT1A1*28 polymorphism may not be a suitable biomarker to predict irinotecan (IRI)-induced toxicities and chemotherapy tumour response (TR) in Asians, while UGT1A1*6 polymorphism is associated with a higher risk of IRI-induced neutropenia and diarrhoea, but not IRI-based chemotherapy TR.'</td></tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>*28/*28: E
*1/*28: AA

PM: E
IM: E</td>
<td>
<table>
<tr><td>diarrhoea</td><td>OR = 5.93 (1.46-24.0) (S)</td><td>NS</td><td rowspan="2">11%</td></tr>
<tr><td></td><td colspan="2">The association was also significant for *28/*28 versus *1/*1+ *1/*28 (OR = 6.25 (1.51-25.0) (S)) (3 studies with 131 patients of which 8 *28/*28).</td></tr>
<tr><td>neutropenia</td><td>NS</td><td>NS</td><td rowspan="2">30%</td></tr>
<tr><td></td><td colspan="2">There was also no significant association for *28/*28 versus *1/*1+*1/*28 (NS) (2 studies with 101 patients of which 5 *28/*28) and for *1/*28+*28/*28 versus *1/*1 (NS) (8 studies with 494 patients of which 95 *1/*28+ *28/*28).</td></tr>
<tr><td>tumour response</td><td colspan="2">NS for *1/*28+*28/*28 versus *1/*1</td><td>54%</td></tr>
<tr><td colspan="4">There was no statistically significant heterogeneity between the studies.</td></tr>
</table>

<table>
<tr><td colspan="4">ORs (95% CI) for *1/*6 and *6/*6 versus *1/*1:</td></tr>
<tr><td></td><td>*6/*6</td><td>*1/*6</td><td>incidence for *1/*1 (% of patients)</td></tr>
<tr><td>diarrhoea</td><td>OR = 17.6 (2.58-121) (S)</td><td>OR = 4.36 (1.74-10.9) (S)</td><td rowspan="2">8%</td></tr>
<tr><td></td><td colspan="2">The association was also significant for *6/*6 versus *1/*1+*1/*6 (OR = 5.26 (1.85-14.3) (S)) (5 studies with 307 patients of which 17 *6/*6).</td></tr>
<tr><td>neutropenia</td><td>NS</td><td>NS</td><td rowspan="2">26%</td></tr>
<tr><td></td><td colspan="2">The association was significant for *6/*6 versus *1/*1+*1/*6 (OR = 5.00 (1.69-14.3) (S)) (4 studies with 277 patients of which 17 *6/*6).
The association was also significant for *1/*6+*6/*6 versus *1/*1 (OR = 2.40 (1.28-4.49) (S)) (4 studies with 233 patients of which 75 *1/*6+*6/*6).</td></tr>
<tr><td>tumour response</td><td colspan="2">NS for *1/*6+*6/*6 versus *1/*1</td><td>59%</td></tr>
<tr><td colspan="4">There was no statistically significant heterogeneity between the studies.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Liu XH et al. Predictive value of UGT1A1*28 polymorphism in irinotecan-based chemotherapy.
J Cancer 2017;8:691-703.
PubMed PMID: 28367249.</td>
<td>4</td>
<td>Meta-analysis of 57 clinical trials (58 studies) with in total 6087 patients treated with irinotecan, either as combined chemotherapy or as monotherapy. Irinotecan doses in the studies varied from 60 to 375 mg/m^2. Patients were Caucasian in 15 studies, Asian in 40 studies and of mixed ethnicities or not reported in 2 studies. Patients had metastatic colorectal cancer in 29 studies, mixed tumours in 6 studies, metastatic non-small cell lung cancer in 5 studies, advanced gastric cancer in 3 studies, small cell lung cancer in 2 studies, advanced oesophageal cancer in 2 studies and another type of cancer in the remaining 11 studies. The quality of the included studies scored 7-9 points on the 9-point Newcastle-Ottawa Scale.
Of the 57 publications included in the meta-analysis, 11 were also included separately in this risk analysis (Kweekel 2008,</td>
<td>Authors' conclusion: 'Our data showed that the UGT1A1*28 polymorphism had a significant relationship with toxicity and response to irinotecan-based chemotherapy. This polymorphism may be useful as a monitoring index for cancer patients receiving irinotecan-based</td>
</tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td></td>
<td>Liu 2008, Han 2006, de Jong 2006, Massacesi 2006, Toffoli 2006, Innocenti 2004, Marcuello 2004, Rouits 2004, Font 2003 and Iyer 2002). A later publication of one study was also included in the meta-analysis (McLeod 2006).
Of the 57 publications included in the meta-analysis, 17 were also included in the meta-analysis of Hu 2010 Eur J Cancer, 13 in the meta-analysis of Liu 2014, 10 in the meta-analysis of Hu 2010 Clin Cancer Res, 9 in the meta-analysis of Han 2014, 8 in the meta-analyses of Liu 2013 and Dias 2012, 7 in the meta-analyses of Dias 2014 and Hoskins 2007, and 5 in the meta-analysis of Chen 2014.
Data on diarrhoea were derived from 44 studies including a total of 4868 patients. The comparison between *1/*28 and *1/*1 was based on 3435 patients from 28 studies. The comparison between *28/*28 and *1/*1 was based on 2610 patients from 17 studies of which 151 *28/*28.
Data on neutropenia were derived from 49 studies including a total of 5232 patients. The comparison between *1/*28 and *1/*1 was based on 3948 patients from 32 studies. The comparison between *28/*28 and *1/*1 was based on 3575 patients from 27 studies of which 219 *28/*28.
Data on tumour response were derived from 18 studies including a total of 2024 patients.
Toxicity was defined as severe toxicity and tumour response as partial or complete remission.
A random-effects model was used for the meta-analysis in case of significant heterogeneity ($p < 0.1$). Otherwise, a fixed-effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias was determined by Egger's and Begg's tests. In case of publication bias (a significant Egger's test), a trim and fill method was carried out for adjusting. Publication bias analyses were performed for all comparisons, but not for the subgroups.

Results:
<table>
<tr><td colspan="4">ORs (95% CI) versus *1/*1:</td></tr>
<tr><td></td><td>*28/*28</td><td>*1/*28</td><td>incidence for *1/*1 (% of patients)</td></tr>
<tr><td colspan="4">Diarrhoea</td></tr>
<tr><td>all patients</td><td>OR = 3.97 (1.88-8.38) (S)</td><td>OR = 1.56 (1.25-1.96) (S)</td><td>9.3%</td></tr>
<tr><td></td><td colspan="2">The association was also significant for *28/*28 versus *1/*1+ *1/*28 (OR = 3.64 (2.01-6.58) (S)) (24 studies with 3175 patients).</td><td></td></tr>
<tr><td>Caucasian patients</td><td>NS</td><td>NS</td><td>13%</td></tr>
<tr><td></td><td colspan="2">The association was significant for *28/*28 versus *1/*1+ *1/*28 (OR = 1.62 (1.03-2.53) (S)) (10 studies with 1211 patients).
The association did not reach significance for *1/*28+*28/*28 versus *1/*1 (NS) (11 studies with 1214 patients).</td><td></td></tr>
<tr><td>Asian patients</td><td>OR = 8.98 (5.21-15.5) (S)</td><td>OR = 1.85 (1.37-2.50) (S)</td><td>8.2%</td></tr>
</table>
</td>
<td>chemotherapy.'</td>
</tr>
</table>

ref. 4, continuation			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 8.64 (4.14-18.0) (S)) (13 studies with 1917 patients).		
		colorectal cancer patients	OR = 3.53 (1.54-8.09) (S)	OR = 1.60 (1.11-2.31) (S)	
			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 3.16 (1.61-6.19) (S)) (17 studies with 2656 patients).		
		non-small cell lung cancer patients	-	NS	
			The association was also not significant for *1/*28+*28/*28 versus *1/*1 (NS) (4 studies with 321 patients).		
		small cell lung cancer patients	-	NS	
			The association was significant for *28/*28 versus *1/*1+*1/*28 (OR = 19.90 (2.57-154) (S)) (2 studies with 64 patients) and for *1/*28+*28/*28 versus *1/*1 (OR = 3.95 (1.42-11.0) (S)) (3 studies with 131 patients).		
		Neutropenia			
	*28/*28: E *1/*28: E	all patients	OR = 5.34 (3.05-9.33) (S)	OR = 1.71 (1.41-2.08) (S)	14%
			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 4.12 (2.36-7.20) (S)) (28 studies with 3668 patients).		
		Caucasian patients	OR = 5.39 (3.43-8.47) (S)	OR = 1.86 (1.34-2.60) (S)	11%
			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 3.39 (1.92-5.98) (S)) (12 studies with 1455 patients).		
		Asian patients	OR = 4.77 (1.71-13.2) (S)	OR = 1.56 (1.07-2.27) (S)	16%
			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 4.16 (1.44-12.0) (S)) (15 studies with 2154 patients).		
		colorectal cancer patients	OR = 5.07 (2.56-10.0) (S)	OR = 1.76 (1.40-2.23) (S)	
			The association was also significant for *28/*28 versus *1/*1+*1/*28 (OR = 3.70 (1.88-7.30) (S)) (20 studies with 2894 patients).		
		non-small cell lung cancer patients	-	NS	
			There was a trend for an increased risk for *1/*28+*28/*28 versus *1/*1 (p = 0.064, NS) (4 studies with 351 patients).		
		Tumour response			
	*1/*28 + *28/*28: AA[#]	all patients	OR = 1.20 (1.07-1.34) (S) for *1/*28+*28/*28 versus *1/*1		

ref. 4, continuation		Caucasian patients	OR = 1.23 (1.06-1.42) (S) for *1/*28+*28/*28 versus *1/*1		
		Asian patients	NS for *1/*28+*28/*28 versus *1/*1		
		colorectal cancer patients	OR = 1.24 (1.05-1.48) (S) for *1/*28+*28/*28 versus *1/*1		
		non-small cell lung cancer patients	NS for *1/*28+*28/*28 versus *1/*1		
		small cell lung cancer patients	NS for *1/*28+*28/*28 versus *1/*1		
		prospective studies (12 studies, 1292 patients)	NS for *1/*28+*28/*28 versus *1/*1		
		retrospective studies (4 studies, 538 patients)	OR = 1.54 (1.06-2.23) (S) for *1/*28+*28/*28 versus *1/*1		
		For diarrhoea, there was a statistically significant heterogeneity between the studies for the following comparisons: - all patients, *28/*28 versus *1/*1 - all patients, *28/*28 versus *1/*1+*1/*28 - Caucasian patients, *1/*28+*28/*28 versus *1/*1 - colorectal cancer patients, *28/*28 versus *1/*1 - colorectal cancer patients, *1/*28 versus *1/*1 - colorectal cancer patients, *28/*28 versus *1/*1+*1/*28 For the comparisons for all patients, ethnicity and year of publication together accounted for over 90% of the heterogeneity.			
		For neutropenia, there was a statistically significant heterogeneity between the studies for the following comparisons: - all patients, *28/*28 versus *1/*1 - all patients, *28/*28 versus *1/*1+*1/*28 - Caucasian patients, *28/*28 versus *1/*1+*1/*28 - Asian patients, *1/*28 versus *1/*1 - Asian patients, *28/*28 versus *1/*1 - Asian patients, *28/*28 versus *1/*1+*1/*28 - colorectal cancer patients, *28/*28 versus *1/*1 - colorectal cancer patients, *28/*28 versus *1/*1+*1/*28 For the comparisons for all patients, *28/*28 versus *1/*1+*1/*28, the number of patients accounted for 25% of the heterogeneity and no other factors were found.			
		For tumour response, there was a statistically significant heterogeneity between the studies for the following comparisons: - all patients - Asian patients - colorectal cancer patients - retrospective studies			
		There was no publication bias for any of the comparisons mentioned above.			
		Results for all patients were not affected by omitting individual studies in the meta-analyses.			
		For the comparison of *1/*28+*28/*28 versus *1/*1 for all patients, the required sample size for diarrhoea, neutrope-			

<table>
<tr><td>ref. 4, continuation</td><td></td><td>nia and tumour response was respectively 763, 1162 and 1078 patients. The number of patients in these meta-analyses were higher.</td><td></td></tr>
<tr><td>ref. 5
Lu CY et al. Clinical implication of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab combined with FOLFIRI in the first-line setting. Transl Oncol 2015;8:474-9. PubMed PMID: 26692528.</td><td>3</td><td>70 patients with metastatic colorectal cancer and a life expectancy of more than 3 months were treated with bevacizumab plus FOLFIRI (folinic acid, 5-fluorouracil and irinitotecan) and followed for a period of 6 to 34 months (median 22 months).
The initial irinotecan dose was 180 mg/m^2 every 2 weeks for patients with the *1/*1 or *1/*28 genotype and 120 mg/m^2 every two weeks (67% of the normal dose) for patients with the *28/*28 genotype. The dose of irinotecan was escalated by 20 to 30 mg/m^2 every two cycles until grade 3/4 adverse events occurred or until the maximum dose of 260 mg/m^2 for *1/*1, 240 mg/m^2 for *1/*28 and 210 mg/m^2 for *28/*28 (81% of the maximum dose for *1/*1 and 88% of the maximum dose of *1/*28) was reached.
After the first two treatment cycles, haematological and non-haematological adverse events (including neutropenia, diarrhoea, and nausea/vomiting) were assessed.
The response to treatment was assessed radiologically, and the best response was recorded. The first response assessment was usually after the fourth or sixth cycle. Complete response was defined as the disappearance of all target lesions. Partial response was defined as at least a 30% decreese in the sum of the longest diameter from baseline. Progressive disease was defined as either at least a 20% increase in the sum of the longest diameter of target lesions, with the smallest sum of the longest diameters recorded before treatment as reference or the identification of one or more new lesions. Stable disease was defined as neither sufficient shrinkage to quality for partial response nor sufficient increase to qualify for progressive disease. The best response was defined as the best result recorded by the investigators because the confirmatory imaging evidence of response obtained after four to six cycles of chemotherapy was not consistently available.
The primary end points were response rate and progression-free survival. The secondary endpoints were toxicity and overall survival.
For liver/lung metastatic lesions, metastasectomy was performed after a multidisciplinary team meeting (25.7% of patients). Patients who underwent metastasectomy achieved better overall survival than those who did not. The comparisons between *28/*28 and *1/*1+*1/*28 were not adjusted for metastasectomy.

Genotyping:
- 65x *1/*1+*1/*28
- 5x *28/*28

Results:
Results for *28/*28 on reduced initial dose compared to *1/*1+*1/*28 on normal initial dose:
<table><tr><td></td><td>*28/*28</td><td>value for *1/*1+ *1/*28 (incidence in % of patients or maximum dose)</td></tr></table></td><td>Authors' conclusion: 'For patients with the UGT1A1 *28/*28 genotype, the starting dose of irinotecan should be decreased to diminish the adverse events of irinotecan. …
Our study showed that mCRC patients with UGT1A1 *1/*1 and *1/*28 genotypes could receive escalated doses of irinotecan to obtain a more favorable clinical outcome without significant AEs.'</td></tr>
</table>

<table>
<tr><td>ref. 5, continuation</td><td>*28/*28: A</td><td>
<table>
<tr><td colspan="2">response (either complete or partial)</td><td>x 0.26 (S)</td><td>77%</td></tr>
<tr><td colspan="2" rowspan="2">disease control rate (either response or stable disease)</td><td>x 0.43 (S)</td><td rowspan="2">94%</td></tr>
<tr><td>The majority of *1/*1+*1/*28 patients (74%) had had a partial response, the majority of *28/*28 patients (60%) had progressive disease.</td></tr>
<tr><td colspan="2">progression-free survival</td><td>S for *28/*28 versus *1/*28 versus *1/*1 (increase with the number of *1-alleles)</td><td></td></tr>
<tr><td colspan="2">adverse events grade 3/4</td><td>x 9.7 (S)</td><td>6.2%</td></tr>
<tr><td rowspan="2">maximum irinotecan dose tolerated</td><td>mean</td><td>x 0.76 (156 mg/kg) (S)</td><td>206 mg/kg</td></tr>
<tr><td>largest group (40% of patients)</td><td>x 0.67 (120 mg/kg) (S)</td><td>180 mg/kg</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 6
Dias MM et al. The effect of the UGT1A1*28 allele on survival after irinotecan-based chemotherapy: a collaborative meta-analysis. Pharmacogenomics J 2014;14:424-31. PubMed PMID: 24709690.</td><td>4</td><td>Meta-analysis of 11 observational cohort studies (from 10 publications) with in total 1823 patients treated with irinotecan, either as combined chemotherapy or as monotherapy. FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) was the most commonly administered regimen. Irinotecan doses in the studies varied from 60 mg/m^2 weekly to 350 mg/m^2 every 3 weeks. Additional data were provided for 7 publications through correspondence with the primary study investigators.
Of the 10 publications included in the meta-analysis, 3 were also included separately in this risk analysis (Marcuello 2004, Toffoli 2006, Kweekel 2008). A later version of the publication with two cohort studies (McLeod, 2006) was also included in the meta-analysis.
Of the 10 publications in this meta-analysis, 7 were also included in the meta-analyses of Liu 2013 and Dias 2012. The meta-analyses of Liu 2014, Han 2014, Chen 2014, Hu 2010 Clin Cancer Res, Hu 2010 Eur J Cancer and Hoskins 2007 did not investigate clinical efficacy.
Data on overall survival were derived from 10 studies including a total of 1677 patients. The unadjusted comparison between *1/*28 and *1/*1 was based on 1229 patients from 9 studies of which 605 *1/*28. The adjusted comparison was based on 1040 patients from 7 studies of which 528 *1/*28. The unadjusted comparison between *28/*28 and *1/*1 was based on 919 patients from 10 studies of which 158 *28/*28. The adjusted comparison was based on 626 patients from 7 studies of which 98 *28/*28.
Data on progression-free survival were derived from 10 studies including a total of 1494 patients. The unadjusted comparison between *1/*28 and *1/*1 was based on 1360 patients from 10 studies of which 677 *1/*28. The adjusted comparison was based on 1171 patients from 8 studies of which 584 *1/*28. The unadjusted comparison between *28/*28 and *1/*1 was based on 817 patients from 10 studies of which 134 *28/*28. The adjusted comparison was based on 700 patients from 8 studies of which 113 *28/*28.
The primary end point was overall survival, the secondary end point was progression-free survival. Time to progression, the time from initiation of irinotecan until objective tumour progres-</td><td>Authors' conclusion: 'In conclusion, the study demonstrates that UGT1A1*28 is unlikely to be strongly prognostic of overall survival for individuals treated with irinotecan. This is in contrast to the strong association previously reported between UGT1A1 *28 and irinotecan-related toxicity.'</td></tr>
</table>

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<tr>
<td>ref. 6, continuation</td>
<td>*28/*28: AA
*1/*28: AA</td>
<td>
sion, with censoring of death not related to cancer, was used if progression-free survival data were not available.
Hazard ratios or adjusted hazard ratios were calculated for overall and progression-free survival and risks differences for cycles with reduced irinotecan dose.
A random-effects model was used for the meta-analyses of genotype and survival outcomes. A fixed-effects model was used for meta-analyses on the effect of subgroups.
The objectives and methods of this collaborative review were prespecified in a study protocol, of which a copy is available on request. The search and selection strategy was transparent and the data extraction was standardised.
The authors reported which of the included studies confirmed to each of 22 quality criteria.
Publication bias was analysed for all comparisons, but only for overall survival and progression-free survival, not for one of more cycles with reduced irinotecan dose. Publication bias was not analysed for the subgroups.

Results:
<table>
<tr><td colspan="3">Risk versus *1/*1:</td></tr>
<tr><td></td><td>*28/*28</td><td>*1/*28</td></tr>
<tr><td>overall survival</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td colspan="2">Similar results were found for the adjusted HRs (both NS).
Similar results were found for all analysed subgroups (colorectal cancer only, high dose (≥ 250 mg/m^2 every 3 weeks), intermediate dose (150-<250 mg/m^2 every 2 or 3 weeks), low dose (< 150 mg/m^2 weekly), treatment with irinotecan and antimetabolites, treatment with irinotecan and platinum compounds, irinotecan monotherapy, 1st line therapy, 2nd & 3rd line therapy) (NS).</td></tr>
<tr><td>progression-free survival</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td colspan="2">Similar results were found for the adjusted HRs (both NS).
Similar results were found for all analysed subgroups (colorectal cancer only, high dose (≥ 250 mg/m^2 every 3 weeks), intermediate dose (150-<250 mg/m^2 every 2 or 3 weeks), low dose (< 150 mg/m^2 weekly), treatment with irinotecan and antimetabolites, treatment with irinotecan and platinum compounds, irinotecan monotherapy, 1st line therapy, 2nd & 3rd line therapy) (NS). A better progression-free survival in *1/*28 compared to *1/*1 was found in the subgroup with 1st line therapy after adjusting (HR_{adj} = 0.82; 95% CI: 0.69-0.98) (S). However, this was not confirmed by a significant interaction between 1st line and 2nd & 3rd line (NS).</td></tr>
<tr><td>one of more cycles with reduced irinotecan dose</td><td>NS</td><td>Trend for an increased risk (p = 0.07) (NS)</td></tr>
<tr><td colspan="3">For overall survival, there was no statistically significant</td></tr>
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<td></td>
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</table>

ref. 6, continuation		heterogeneity between the studies, but there was a strong trend for statistically significant heterogeneity for the unadjusted comparison between *28/*28 and *1/*1 (p = 0.10). In addition, there was significant heterogeneity for the subgroups low dose and treatment with irinotecan plus platinum compounds for the comparison between *28/*28 and *1/*1. For progression-free survival, there was no statistically significant heterogeneity between the studies for the comparison between *1/*28 and *1/*1, but there was moderate and significant heterogeneity for the comparison between *28/*28 and *1/*1 (p = 0.08). For the unadjusted comparison of the latter, moderate heterogeneity was also found for the subgroups therapy with irinotecan and antimetabolites and 1st line therapy, whereas there was a trend (p = 0.10) for the subgroup colorectal cancer only. For the adjusted comparison, there was no significant heterogeneity for the total group and the subgroups mentioned above, but there was a strong and significant heterogeneity for 2nd and 3rd line therapy. There were indications for publication bias or small-study effects for the adjusted overall survival comparison of *28/*28 versus *1/*1. This was attributable to the study of Lara 2009, but exclusion of this study from the meta-analysis did not substantially alter the results. There were no indications of publication bias or small-study effects for other comparisons. 8 studies were excluded from the meta-analysis, due to insufficient quantitative data, but included in the systematic review. None of these studies reported a difference in overall and progression-free survival between genotypes (NS).	
ref. 7 Han FF et al. Associations between UGT1A1*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol 2014;73:779-88. PubMed PMID: 24519753.	3	Meta-analysis of 19 studies with in total 1671 Asian patients treated with irinotecan, either as combined chemotherapy or as monotherapy. Irinotecan doses in the studies varied from 50 mg/m^2 on day 1, 8 and 15 every 4 weeks to 350 mg/m^2. Of the 19 studies included in the meta-analysis, 2 were also included separately in this risk analysis (Han 2006 and Minami 2007). Of the 19 studies in this meta-analysis, 13 were included in the meta-analysis of Chen 2014. The meta-analyses of Liu 2014, Hu 2010 Clin Cancer Res and Hoskins 2007 did not investigate Asian patients. The meta-analyses of Liu 2013, Dias 2012, Hu 2010 Eur J Cancer did not investigate neutropenia risk. The comparison between *28/*28 + *6/*28 + *6/*6 and *1/*28 + *1/*6 + *1/*1 was based on 923 patients from 11 studies. The comparison between *6/*6 and *1/*6 + *1/*1 was based on 984 patients from 7 studies. Neutropenia was defined as neutropenia grade 3-4 or neutropenia grade 4. A fixed-effects model was used for the meta-analyses, because there was no significant heterogeneity between the studies (p > 0.1). This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. The authors indicate that the quality of the included studies was assessed, but do not present the assessment results. Publication bias analyses were performed for all comparisons. Results: Neutropenia risk compared to either *1/*28 + *1/*6 + *1/*1 or *1/*6 + *1/*1:	Authors' conclusion: 'In conclusion, the UGT1A1*6 and UGT1A1*6/*28 genotypes were associated with an increased risk of irinotecan-induced neutropenia in Asian cancer patients.'

<table>
<tr>
<td>ref. 7, continuation</td>
<td>*28/*28 + PM: E

PM: E</td>
<td>
<table>
<tr><td>*28/*28 + *6/*28 + *6/*6</td><td>OR = 3.28 (95% CI: 2.15-4.98) (S)</td></tr>
<tr><td rowspan="2">*6/*6</td><td>OR = 3.28 (95% CI: 1.89-5.69) (S)</td></tr>
<tr><td>The risk was also increased for *6/*6 + *1/*6 compared to *1/*1: OR = 1.54 (95% CI: 1.18-2.04) (S) (9 studies with in total 994 patients)</td></tr>
<tr><td colspan="2">There was no statistically significant heterogeneity between the studies.
There were no indications for publication bias. However, for the comparison of *6/*6 with *1/*6 + *1/*1, the OR was influenced by leaving individual studies out.</td></tr>
</table>
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<td></td>
</tr>
<tr>
<td>ref. 8
Chen YJ et al. The association of UGT1A1*6 and UGT1A1*28 with irinotecan-induced neutropenia in Asians: a meta-analysis. Biomarkers. 2014;19:56-62. PubMed PMID: 24308720.</td>
<td>3

*28 + *6: E</td>
<td>
Meta-analysis of 18 clinical trials with in total 1303 Asian patients treated with irinotecan. Irinotecan doses in the studies varied from 30 to 350 mg/m^2.
Of the 18 studies included in the meta-analysis, 1 was also included separately in this risk analysis (Minami 2007).
Of the 18 studies in this meta-analysis, none were included in earlier meta-analyses. The meta-analyses of Liu 2014, Hu 2010 Clin Cancer Res and Hoskins 2007 did not investigate Asian patients. The meta-analyses of Liu 2013, Dias 2012, Hu 2010 Eur J Cancer did not investigate neutropenia risk.
The comparison for *28 + *6 was based on 886 patients from 13 studies, of which 335 *1/*28 + *1/*6 and 97 *28/*28 + *6/*28 + *6/*6. The comparison for *28 was based on 658 patients from 6 studies, of which 133 *1/*28 and 15 *28/*28. The comparison for *6 was based on 652 patients from 5 studies, of which 217 *1/*6 and 31 *6/*6.
A model-free generalized odds ratio OR_G was calculated. OR_G was defined such that $OR_G > 1$ if patients with neutropenia grade 3-4 have a higher gene variant load than patients without neutropenia grade 3-4.
A random-effects model was used for the meta-analyses, but prospective registration of the protocol was not mentioned.
The search and selection strategy was transparent and the data extraction was standardised.
Quality of the included studies was not judged.
Publication bias analyses were performed for all comparisons.

Results:
<table>
<tr><td colspan="4">Prevalence of neutropenia per genotype/genotype group and effect of gene variants on neutropenia risk (OR_G):</td></tr>
<tr><td></td><td>*28/*28 and/or *6/*28 and/or *6/*6</td><td>*1/*28 and/or *1/*6</td><td>% of *1/*1 with neutropenia</td></tr>
<tr><td rowspan="2">*28 + *6</td><td>x 2.5</td><td>x 1.4</td><td rowspan="2">24%</td></tr>
<tr><td colspan="2">OR_G = 2.55 (95% CI: 1.82-3.68) (S).
An OR_G of 2.55 indicates that patients with neutropenia grade 3-4 have a 155% higher gene variant load than patients without neutropenia grade 3-4.</td></tr>
<tr><td rowspan="2">*28</td><td>x 2.1</td><td>x 1.3</td><td rowspan="2">25%</td></tr>
<tr><td colspan="2">Trend for $OR_G > 1$ (95% CI: 0.94-2.97) (NS).</td></tr>
<tr><td rowspan="2">*6</td><td>x 1.8</td><td>x 1.5</td><td rowspan="2">23%</td></tr>
<tr><td colspan="2">Trend for $OR_G > 1$ (95% CI: 0.97-3.04) (NS).
However, this trend becomes much weaker (95% CI: 0.85-2.35)</td></tr>
</table>
</td>
<td>Authors' conclusion: 'In Asians, a combination test of UGT1A1*6 and UGT1A1*28 might be a potential biomarker of irinotecan-induced neutropenia, an observation that will need additional trials for confirmation.'</td>
</tr>
</table>

ref. 8, continuation		<table><tr><td></td><td>after reducing heterogeneity to non-significant by removal of one of the studies (Onoue 2009) from the meta-analysis.</td><td></td></tr><tr><td colspan="3">For *28 + *6 and for *28, the heterogeneity between the studies was not significant. For *6, the heterogeneity between the studies was moderate and statistically significant. There were no indications for publication bias.</td></tr><tr><td colspan="3">For *28 + *6, the width of the 95% confidence interval of the OR_G of each study decreased with the study publication year. From 2008 on, the OR_G per publication year differed less than 20% with the OR_G of the subsequent publication year. The number of studies per publication year was maximally 3.</td></tr></table>	
ref. 9 Liu X et al. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. Pharmacogenomics J 2014;14:120-9. PubMed PMID: 23529007.	3 *1/*28: E *28/*28: E	A meta-analysis of 16 studies including a total of 2,328 mainly Caucasian patients with colorectal cancer. Of the 16 studies included in the meta-analysis, 7 were also included separately in this risk analysis (Marcuello, 2004; Rouits, 2004; Carlini, 2005; Massacesi, 2006; Toffoli, 2006; Côté, 2007 and Kweekel, 2008). A later publication of one study is also included in the meta-analysis (McLeod, 2006). The outcome measure was grade 3-4 toxicity. A random-effects model was used for the meta-analysis in case of significant heterogeneity ($p < 0.1$). Otherwise, a fixed-effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. The authors indicate that the quality of the included studies was evaluated based on study design, the detection method of the polymorphisms, chemotherapy regimens, and grading systems for toxicity, but do not present quality scores for the studies. Publication bias analyses were performed for all comparisons and for all subgroups. In case of publication bias, a trim and fill method was carried out for adjusting. *1/*28 versus *1/*1: - Increased risk of neutropenia (OR = 1.90; 95% CI: 1.44-2.51) (S). Similar results were found after correction for publication bias and in the subgroups using irinotecan doses exceeding 150 mg/m^2 and irinotecan doses lower than 150 mg/m^2. There were insufficient studies using therapy without fluorouracil to compare therapy with and without fluorouracil. - No increased risk of diarrhoea (NS). There was a trend towards a higher risk of diarrhoea in the subgroup using irinotecan doses exceeding 150 mg/m^2. *28/*28 versus *1/*1: - Increased risk of neutropenia (OR = 4.79; 95% CI: 3.28-7.01) (S). Similar results were found in the subgroups using therapy without fluorouracil and in those using fluorouracil-based therapy and in the subgroups using irinotecan doses exceeding 150 mg/m^2 (OR = 4.64) and irinotecan doses lower than 150 mg/m^2 (OR = 6.37). - Increased risk of diarrhoea (OR = 1.84; 95% CI: 1.24-2.72) (S). The increased risk of diarrhoea was only observed in studies investigating irinotecan doses exceeding 150 mg/m^2 (OR =	Authors' conclusion: 'This meta-analysis provided evidence for the association between the UGT1A1*28 polymorphism and an increased risk of irinotecan-induced neutropenia and diarrhoea in colorectal cancer. Associations with significant neutropenia were consistent and strong. In contrast, associations with diarrhoea were weaker, and primarily seen when higher doses of irinotecan were administrated.'

ref. 9, continuation		2.37; 95% CI: 1.39-4.04 (S)) or in combination with fluorouracil (OR = 1.78; 95% CI: 1.16-2.75 (S)). Non-fluorouracil-based therapy gave a higher OR than fluorouracil-based therapy, but the increase was not significant. *28/*28 versus (*1/*1+*1/*28): - Increased risk of neutropenia (OR = 3.44; 95% CI: 2.45-4.82) (S). Similar results were found in the subgroup using non-fluorouracil-based therapy and the subgroup using fluorouracil-based therapy and in the subgroups using irinotecan doses exceeding 150 mg/m^2 (OR = 3.34) and irinotecan doses lower than 150 mg/m^2 (OR = 3.63). - Increased risk of diarrhoea (OR = 1.71; 95% CI: 1.18-2.47) (S). The increased risk of diarrhoea was only observed in studies investigating irinotecan doses exceeding 150 mg/m^2 (OR = 2.04; 95% CI: 1.23-3.38 (S)) or in combination with fluorouracil (OR = 1.67; 95% CI: 1.11-2.52 (S)). Non-fluorouracil-based therapy gave a higher OR than fluorouracil-based therapy, but the increase was not significant. N.B.1: *28 is the most common allele variant in the Caucasian population. N.B.2: The most common irinotecan doses used in the Netherlands exceed 150 mg/m^2.	
ref. 10, kinetics Goetz MP et al. UGT1A1 genotype-guided phase I study of irinotecan, oxaliplatin, and capecitabine. Invest New Drugs 2013;31:1559-67. PubMed PMID: 24114122.	3 *1/*28: AA *28/*28: AA	24 patients were treated with the maximum tolerated dose of irinotecan once every 3 weeks in combination with oxaliplatin and capecitabine. The maximum tolerated dose was 150 mg/m^2 for *1/*1 and *1/*28 and 75 or 100 mg/m^2 (both n=3) for *28/*28. Relevant co-medication was not excluded (although antiretroviral therapy was) Genotyping: - 9x *1/*1 - 9x *1/*28 - 6x *28/*28 *1/*28 versus *1/*1: - Dose-corrected SN-38 AUC increased by 4.6% (NS; from 2.33 to 2.44 ng.hour/mL per mg/m^2) *28/*28 versus *1/*1: - Dose-corrected SN-38 AUC increased by 71% (NS; from 2.33 to 3.99 ng.hour/mL per mg/m^2)	Authors' conclusion: 'UGT1A1 genotype affects the dose and pharmacokinetics of the CAPIRINOX regimen.' Dose-corrected SN-38 AUC versus *1/*1: *1/*28: 105% *28/*28: 171% Dose-corrected SN-38 AUC versus all genotypes: *1/*28: 88% *28/*28: 143%
ref. 11 Liu X et al. Association between UGT1A1 *28 polymorphisms and clinical outcomes of irinotecan-based chemotherapies in colorectal cancer: a meta-analysis in Caucasians. PLoS One 2013;8:e58489. PubMed PMID: 23516488.	3	A meta-analysis of 12 studies including a total of 1,896 mainly Caucasian patients with colorectal cancer. Of the 12 studies included in the meta-analysis, 3 were also included separately in this risk analysis (Carlini, 2005; Toffoli, 2006 en Kweekel, 2008). A later publication of one study is also included in the meta-analysis (McLeod, 2006). Therapeutic response was defined as partial or complete response. A fixed-effects model was initially used for the meta-analysis, and confirmatory analyses with a random-effects model were performed in case of potential heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. The authors indicate that the quality of the included studies was evaluated based on study design, polymorphism detection method, combination regimens, line of therapy, and	Authors' conclusion: 'UGT1A1*28 polymorphism cannot be considered as a reliable predictor of therapeutic response and progression-free survival in colorectal cancer patients treated with irinotecan-based chemotherapy. The overall survival relationship with UGT 1A1*28 in the patients with lower-dose irinotecan che-

ref. 11, continuation	*1/*28: AA *28/*28: AA	grading systems for response, but do not present quality scores for the studies. Publication bias analyses were performed for all comparisons and for all subgroups. In case of publication bias, a trim and fill method was carried out for adjusting. *1/*28 versus *1/*1: - No difference in therapeutic response, progression-free survival and death (NS). The same results were found in the subgroups using irinotecan doses exceeding 150 mg/m^2 and irinotecan doses lower than 150 mg/m^2. *28/*28 versus *1/*1: - No difference in therapeutic response, progression-free survival and death (NS). The same results were found on therapeutic response and progression-free survival in the subgroups using irinotecan doses exceeding 150 mg/m^2 and irinotecan doses lower than 150 mg/m^2. An increased mortality rate was found in the subgroup using irinotecan doses lower than 150 mg/m^2 (HR = 1.48; 95% CI: 1.06-2.07) (S). However, these results were only based on two studies, of which only the largest found an effect. *28/*28 versus (*1/*1+*1/*28): - No difference in therapeutic response (NS). The same results were found in the subgroups using irinotecan doses exceeding 150 mg/m^2 and irinotecan doses lower than 150 mg/m^2. N.B.1: *28 is the most common allele variant in the Caucasian population. N.B.2: The most common irinotecan doses used in the Netherlands exceed 150 mg/m^2.	motherapy requires further validation.'
ref. 12 Dias MM et al. Impact of the UGT1A1*28 allele on response to irinotecan: a systematic review and meta-analysis. Pharmacogenomics 2012;13:889-99. PubMed PMID: 22676194.	4 *1/*28: AA *28/*28: AA	A meta-analysis of 12 studies including a total of 1,898 patients. Of the 12 studies included in the meta-analysis, 5 were also included separately in this risk analysis (Carlini, 2005; Han, 2006; Toffoli, 2006; Kweekel, 2008 and Liu, 2008). A later publication of one study was also included in the meta-analysis (McLeod, 2006). Eight of the twelve studies were also included in the meta-analysis by Liu 2013. Response was defined as partial or complete response. A random-effects model was used for the meta-analyses, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised. The authors reported which of the included studies confirmed to each of 45 quality criteria. Publication bias was analysed for all comparisons, but not for the subgroups. *1/*28 versus *1/*1: - No difference in response (NS). *28/*28 versus *1/*1: - No difference in response (NS). (*28/*28+*1/*28) versus *1/*1: - No difference in response (NS).	Authors' conclusion: 'An individual's response to irinotecan is unlikely to be affected by UGT1A1 *28 status.'

ref. 12, continuation		Similar results were found in the subgroups using irinotecan doses ≥ 250 mg/m^2, 150-250 mg/m^2 or < 150 mg/m^2 and in the subgroups of patients with colorectal cancer and lung cancer.	
ref. 13 Hu ZY et al. Dose-dependent association between UGT1A1 *28 genotype and irinotecan-induced neutropenia: low doses also increase risk. Clin Cancer Res 2010;16:3832-42. PubMed PMID: 20562211.	4 *1/*28: E *28/*28: E	A meta-analysis of 15 studies including a total of 1,998 mainly Caucasian patients. Of the fifteen studies included in the meta-analysis, eight were also included separately in this risk analysis (Marcuello, 2004; Rouits, 2004; Carlini, 2005; Massacesi, 2006; McLeod, 2006; Toffoli, 2006; Côté, 2007 and Kweekel, 2008). Ten of the fifteen studies in this meta-analysis were also included in the meta-analysis by Liu 2014. The meta-analysis of the relative extent of glucuronidation covered 9 studies including a total of 581 patients, of which two studies were performed among Asian patients. Meta-analyses were performed with a fixed-effects model. Since, this is only allowed in the absence of significant heterogeneity, this indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. The authors reported which of the included studies confirmed to each of 28 (neutropenia) or 30 (extent of glucuronidation) quality criteria. Publication bias was analysed for all comparisons, but not for the subgroups, except for neutropenia and dose <250 mg/m^2 and for neutropenia and dose 150-250 mg/m^2, which were the only subgroups with 8 or more studies. *1/*28 versus *1/*1: - Increased risk of grade 3-4 neutropenia (RR = 1.43; 95% CI: 1.16-1.77) (S). Similar results were found in the subgroups using irinotecan doses < 150 mg/m^2 (RR = 2.94) and 150-250 mg/m^2 (RR = 1.29). The RR for irinotecan doses ≥ 250 mg/m^2 was based on two studies and was non-significant. - Decreased weighted mean difference (WMD) of the extent of SN-38 glucuronidation (WMD = -1,55; 95% CI: -0.87 to -2.23) (S). Similar results were found for irinotecan doses < 250 mg/m^2 (WMD = -1.85), but the WMD was non-significant for doses ≥ 250 mg/m^2. There was no significant heterogeneity between the studies for any of the comparisons. Egger's test for publication bias was significant for neutropenia for all investigated dose ranges (all doses, doses <250 mg/m^2 and doses of 150-250 mg/m^2), but Begg's test was not. There was no indication for publication bias for the extent of glucuronidation (only investigated for all doses). *28/*28 versus (*1/*1+*1/*28): - Increased risk of grade 3-4 neutropenia (RR = 2.20; 95% CI: 1.82-2.66) (S). Similar results were found in the subgroups using irinotecan doses < 150 mg/m^2 (RR = 2.43) and 150-250 mg/m^2 (RR = 2.00). The risk was higher in the subgroup using irinotecan doses ≥ 250 mg/m^2 (RR = 7.22) than in the subgroup using irinotecan doses < 250 mg/m^2 (S). - Decreased weighted mean difference (WMD) of the extent of SN-38 glucuronidation (WMD = -2.44; 95% CI: -1.73 to -3.14) (S). The difference was greater in the subgroup using irinotecan doses ≥ 250 mg/m^2 (WMD = -3.08) than in the subgroup	Authors' conclusion: 'The UGT1A1 *28/*28 genotype was associated with an increased risk of neutropenia not only at medium or high doses of irinotecan but also at low doses. The dose-dependent manner of SN-38 glucuronidation explained why the association between UGT1A1 *28 and neutropenia was dose dependent.'

ref. 13, continuation		using irinotecan doses < 250 mg/m^2 (WMD = -1.62). There was no significant heterogeneity between the studies for any of the comparisons. Egger's test for publication bias was significant for neutropenia and all doses, but Begg's test was not. There were no indications for publication bias for the investigated dose ranges (doses <250 mg/m^2 and doses of 150-250 mg/m^2). There was no indication for publication bias for the extent of glucuronidation (only investigated for all doses). N.B.1: *28 is the most common allele variant in the Caucasian population. N.B.2: The most common irinotecan doses used in the Netherlands range from 180 to 350 mg/m^2.	
ref. 14 Hu ZY et al. Dose-dependent association between UGT1A1-*28 polymorphism and irinotecan-induced diarrhoea: a meta-analysis. Eur J Cancer 2010;46:1856-65. PubMed PMID: 20335017.	3 *1/*28: E	A meta-analysis of 20 studies including a total of 1,760 patients (1,263 mainly Caucasian, 497 Asian). Of the 20 studies included in the meta-analysis, thirteen were also included separately in this risk analysis (Iyer, 2002; Font, 2003; Innocenti, 2004; Marcuello, 2004; Rouits, 2004; Carlini, 2005; de Jong, 2006; Han, 2006; Massacesi, 2006; Toffoli, 2006; Côté, 2007; Kweekel, 2008 and Liu, 2008). Eight of the twenty studies in this meta-analysis were also included in the meta-analysis by Liu 2014. Meta-analyses were performed with a fixed-effects model. Since, this is only allowed in the absence of significant heterogeneity, this indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. The authors indicate that the quality of the included studies was assessed based on study design, number of patients, source of population, mutation detection method, races, tumour types, chemotherapy regimens and grade criteria for diarrhoea, but do not present the assessment results. Publication bias was analysed for all comparisons for *28, but not for the subgroups, except for doses ≥ 125 mg/m^2 for all patients and for Caucasians, which were the only subgroups with 6 or more studies. Potential publication bias was evaluated by visual examination for possible skewness in funnel plots and Egger's test. The Duval and Tweedie nonparametric trim and fill procedure was performed to further assess the possible effect of publication bias in case of a significant Egger's test. Publication bias analysis was not performed for *6 (only 4 studies). *1/*28 versus *1/*1: - Increased risk of grade 3-4 diarrhoea (OR = 1.73; 95% CI: 1.25-2.40) (S). Similar results were found in the subgroup using irinotecan doses ≥ 125 mg/m^2 (OR = 1.92; 95% CI: 1.31-2.82). The OR was significant at this dose in the subgroup of Caucasian patients, but not in the subgroup of Asian patients (two studies only). No differences were found in the subgroups using irinotecan doses < 125 mg/m^2 (NS). There was no significant heterogeneity between the studies for any of the comparisons. Egger's test showed significant publication bias for Caucasians and dose ≥ 125 mg/m^2, but adjustment for the likely effect of bias using trim and fill gave a pooled OR of 1.74 (95% CI: 1.16-2.59; S), which is only a slight change from the estimate of 1.87 (95% CI: 1.25-2.81; S) without trim and fill. There were no indications for publication bias for all patients	Authors' conclusion: 'Patients carrying UGT1A1*28 allele(s) are at an increased risk of irinotecan-induced severe diarrhoea. This increased risk is only apparent in those who are administrated with medium or high irinotecan doses.'

ref. 14, continuation	*28/*28: E	and all doses and for all patients and doses ≥ 125 mg/m^2. *28/*28 versus *1/*1: - Increased risk of grade 3-4 diarrhoea (OR = 2.23; 95% CI: 1.31-3.81) (S). Similar results were found in the subgroup using irinotecan doses ≥ 125 mg/m^2 (OR = 3.69; 95% CI: 2.00-6.83). No differences were found in the subgroup using irinotecan doses < 125 mg/m^2 (NS). There were no studies investigating *28/*28 versus *1/*1 in Asian patients. Meta-regression analysis of the dependence of the OR on the dose found that the OR increased by 4.30 when the dose increased by 100 mg/m^2. This would give rise to an OR of almost 5 at a dose of 180 mg/m^2 and an OR of more than 13 at a dose of 350 mg/m^2. This linear relationship was only found for *28/*28 versus *1/*1. There was no significant heterogeneity between the studies for any of the comparisons. There were no indications for publication bias for the two investigated comparisons (all doses and doses ≥ 125 mg/m^2). Because all studies concerned Caucasians, there were no ethnicity subgroups. *28/*28 versus (*1/*1+*1/*28): - Increased risk of grade 3-4 diarrhoea at a dose ≥ 125 mg/m^2 (OR = 2.49; 95% CI: 1.42-4.36) (S). The OR was non-significant when all doses were included (NS). No differences were found in the subgroup using irinotecan doses < 125 mg/m^2 (NS). There was no significant heterogeneity between the studies for any of the comparisons. There were no indications for publication bias for the two investigated comparisons (all doses and doses ≥ 125 mg/m^2). Because all studies concerned Caucasians, there were no ethnicity subgroups.	
	PM: E	*6/*6 versus (*1/*1+*1/*6): - Increased risk of grade 3-4 diarrhoea (OR = 3.54; 95% CI: 1.16-10.77) (S). The data were derived from four Asian studies. Analysis of heterogeneity between the studies was not reported. Publication bias analysis was not performed. (*1/*28+*28/*28) versus *1/*1: - Increased risk of grade 3-4 diarrhoea (OR = 1.81; 95% CI: 1.38-2.39) (S). Similar results were found in the subgroups using irinotecan doses ≥ 125 mg/m^2 (all patients, Caucasian patients and Asian patients). No differences were found in the subgroups using irinotecan doses < 125 mg/m^2 (NS). There was no significant heterogeneity between the studies for any of the comparisons. Egger's test showed significant publication bias for Caucasians and dose ≥ 125 mg/m^2, but adjustment for the likely effect of bias using trim and fill gave a pooled OR of 1.78 (95% CI: 1.28-2.49; S), which also indicates a significantly increased risk of toxicity (OR without trim and fill was 1.93 (95% CI: 1.38-2.70; S)). There were no indications for publication bias for all patients and all doses and for all patients and doses ≥ 125 mg/m^2.	

ref. 14, continuation		NOTE1: *28 is the most common allele variant in the Caucasian population. *6 is relatively common in Asian patients. N.B.2: The most common irinotecan doses used in the Netherlands range from 180 to 350 mg/m^2.	
ref. 15, kinetics Denlinger CS et al. Pharmacokinetic analysis of irinotecan plus bevacizumab in patients with advanced solid tumors. Cancer Chemother Pharmacol 2009;65:97-105. PubMed PMID: 19415281.	4 *1/*28: A *28/*28: A	29 patients were treated with irinotecan 180 mg/m^2 once every two weeks in combination with fluorouracil and folinic acid. Co-medication was excluded. Genotyping: - 9x *1/*1 - 15x *1/*28 - 5x *28/*28 *1/*28 versus *1/*1: - Dose-corrected SN-38 AUC$_{0\text{-}48h}$ increased by 4.8% (S; from 1.65 to 1.73 ng.hour/mL per mg/m^2) *28/*28 versus *1/*1: - Dose-corrected SN-38 AUC$_{0\text{-}48h}$ increased by 109% (S; from 1.65 to 3.45 ng.hour/mL per mg/m^2)	Authors' conclusion: 'UGT1A1 polymorphisms were associated with variability in irinotecan pharmacokinetics.' Dose-corrected SN-38 AUC versus *1/*1: *1/*28: 105% *28/*28: 209% Dose-corrected SN-38 AUC versus all genotypes: *1/*28: 86% *28/*28: 172%
ref. 16 Kweekel DM et al. UGT1A1*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study. Br J Cancer 2008;99:275-82.	3 *28/*28: E *1/*28: E	218 patients, 80 (3x *28/*28, 31x *1/*28, 46x *1/*1) received irinotecan 350 mg/m^2 every three weeks, 138 (11x *28/*28, 62x *1/*28, 65x *1/*1) received irinotecan 350 mg/m^2 every three weeks plus capecitabine, chemotherapy regimens were fully known, but other co-medication was not, tumour evaluation was performed after every three cycles; *clinical endpoints* *1/*1 versus *1/*28 versus *28/*28: - Increased prevalence of febrile neutropenia for both monotherapy and combination therapy (S; 2.2% versus 19.4% versus 0% en 1.5% versus 6.5% versus 18.2% respectively). - No significant differences in the prevalence of grade 3-4 diarrhoea and the prevalence of all grade 3-4 toxicity for monotherapy or combination therapy. - No significant differences in the prevalence of dose reduction after cycle 1, dose per cycle and total dose for monotherapy or combination therapy. (The dose was mainly reduced in cycles 2 and 3 and 89% was due to gastrointestinal toxicity). - No significant differences in the prevalence of complete and partial response for monotherapy or combination therapy. - No significant differences in the prevalence of patients without disease progression for monotherapy or combination therapy.	Authors' conclusion: 'We observed that the UGT1A1*28 genotype is associated with an enhanced risk of febrile neutropenia but not with IRI dose reductions. However, upfront dose reduction may result in a lower incidence of febrile neutropenia in these patients.'
ref. 17 Liu CY et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colo-	3 (*28/*28 + *1/*28): E	128 patients, 6x *28/*28, 20x *1/*28, 102x *1/*1, received irinotecan 180 mg/m^2 every two weeks for 12 cycles as part of first-line therapy with IFL[a], other co-medication not known, median follow-up was 18 months, tumour evaluation was performed after every fourth cycle; *clinical endpoints* (*28/*28 + *1/*28) versus *1/*1: - Prevalence of grade 3-4 neutropenia increased by 998% (S; from 4.9% to 53.8%). - Prevalence of febrile neutropenia increased by 887% (S; from 3.9% to 38.5%).	Authors' conclusion: 'The current data suggested that the UGT1A1*28 polymorphism may be a key determinant for predicting irinotecan-induced severe toxicities without affecting treatment outcome for patients with metastatic colo-

rectal carcinoma. Cancer 2008;112:1932-40. **ref. 17, continuation**		- Prevalence of diarrhoea increased by 356% (S; from 5.9% to 26.9%). - Prevalence of hospitalisation for febrile neutropenia or grade 3-4 diarrhoea increased by 468% (S; from 8.8% to 50%). - Prevalence of treatment-related mortality increased by 475% (S; from 2% to 11.5%). - Prevalence of elevated bilirubin levels before the treatment increased by 163% (S; from 8.8% to 23.1%). - Need for dose reduction increased by 233% (S; from 12.7% to 42.3% of the patients). Dose reduction was equally as often due to febrile neutropenia as due to intolerable diarrhoea. - No significant differences in the response rate, progression-free survival and overall survival. N.B.: No genotyping was performed for the *6 allele, which is common among Asian populations.	rectal cancer.'
ref. 18 Lankisch TO et al. Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyl-transferase 1A7 variants increases risk. Cancer Epidemiol Biomarkers Prev 2008;17:695-701.	3 (*28/*28 + *1/*28): AA	96 patients without clinical diagnoses of Gilbert's syndrome, 58x (*28/*28 + *1/*28), 38x *1/*1, received irinotecan 80 mg/m^2 every week for 12 weeks in combination with either oxaliplatin or 5-fluorouracil and folic acid, other co-medication not known; *clinical endpoints* No significant association of the *28 allele with diarrhoea, anaemia, thrombocytopenia, leukopenia, loss of body weight and irinotecan dose reduction.	Authors' conclusion: 'Our data derived from one of the largest pharmacogenomic study cohorts of irinotecan-treated individuals to date corroborate data from different studies that have failed to find hematologic or gastrointestinal drug toxicity in patients carrying the UGT1A1*28 allele and suggest that additional risk factors may play a permissive role.'
ref. 19 Hoskins JM et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 2007;99:1290-5.	3 *28/*28: E *28/*28:	Meta-analysis of nine studies, of which eight have also been included in this risk analysis, 821 patients, 84x *28/*28, 737x (*1/*28 + *1/*1), irinotecan doses ranged from 80 mg/m^2 per week to 350 mg/m^2 every three weeks. Meta-analyses were performed with a random-effects model, but preregistration of the protocol (including the statistical analysis) was not mentioned. The search and selection strategy and the method of data extraction were not mentioned either. Assessment of the quality of the included studies was not reported. Publication bias was analysed by funnel plot only and for haematological toxicity and all doses only, *clinical endpoints* *28/*28 versus (*1/*28 + *1/*1): - Increased risk of grade 3-4 haematological toxicity at high doses (>250 mg/m^2) (S; OR = 27.8 (95% CI 4.0 – 195)). - Increased risk of grade 3-4 haematological toxicity at medium doses (150-250 mg/m^2) (S; OR = 3.22 (95% CI 1.52 – 6.81)). - No significantly increased risk of grade 3-4 haematological toxicity at low doses (<150 mg/m^2) (NS). - No significantly increased risk of grade 4 diarrhoea indepen-	Authors' conclusion: 'The risk of experiencing irinotecan-induced hematologic toxicity for patients with a UGT1A1 *28/*28 genotype thus appears to be a function of the dose of irinotecan administered.'

ref. 19, continuation	AA	dent of dose (NS). There was no heterogeneity between the studies (most probably only tested for grade 3-4 haematological toxicity and all doses). There was no evidence for publication bias for the only investigated comparison: grade 3-4 haematological toxicity and all doses.	
ref. 20 Minami H et al. Irinotecan pharmacokinetics/ pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics 2007;17:497-504.	3 IM: E PM: E	176 patients, 4x *28/*28, 26x *1/*28, 55x *1/*1, 5x *6/*6, 32x *1/*6, 7x *6/*28, 5x *60/*60, 25x *1/*60, 9x *6/*60, 8x *28/*60, received monotherapy (n = 56) or combination therapy with irinotecan, doses of irinotecan ranged from 100 mg/m^2 per week to 150 mg/m^2 every three weeks. Association of genotype with AUC was determined for all patients, association with toxicity only for patients using monotherapy. The effect of *28 and *6 on AUC was similar. *clinical endpoints* 0 versus 1 versus 2 *28 or *6 alleles: - Increased incidence of grade 3-4 neutropenia (S; 14% versus 24% versus 80%). - No association with the incidence of diarrhoea. *kinetic endpoints* *1/*28 versus *1/*1: - Median SN-38G/SN-38 AUC ratio decreased by 40% (S; from 6.13 to 3.65). 1x (*28 or *6) versus *1/*1: - Dose-corrected SN-38 AUC increased by 40% (S; determined from the slope of the regression line). *28/*28 versus *1/*1: - Median SN-38G/SN-38 AUC ratio decreased non-significantly by 40% (NS; from 6.13 to 3.65). 2x (*28 or *6) versus *1/*1: - Dose-corrected SN-38 AUC increased by 140% (S; determined from the slope of the regression line). *1/*1 versus *28/*1 versus *28/*28: - Significant gene-dose effect of the *28 allele on the median SN-38G/SN-38 AUC ratio (S). N.B.: Genotyping was performed for the most common alleles in Asian populations (*6, *28 and *60). The effect of *60 and *1 on metabolic ratio was not significantly different.	Authors' conclusion: 'The haplotypes significantly associated with reduced area under concentration curve ratios and neutropenia contained UGT1A1 *6 or *28, and both of them should be genotyped before irinotecan is given to Japanese and probably other Asian patients.'
ref. 21 Stewart CF et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. J Clin Oncol 2007;25:2594-600.	3 *28/*28: AA *1/*28: AA	72 paediatric patients, 9x *28/*28, 36x *1/*28, 27x *1/*1, received oral or intravenous irinotecan doses ranging from 15-75 mg/m^2 per day 5 days/week for two weeks as monotherapy or as combination therapy. *clinical endpoints* - No association of *28 with the incidence of grade 3-4 neutropenia or diarrhoea. - Bilirubin levels before treatment were elevated in *28/*28 patients (S; from 0.3-0.4 to 0.6 mg/dL). *kinetic endpoints* *1/*1 versus *28/*1 versus *28/*28: - Increased SN-38 AUC (NS). - Decreased SN-38G/SN-38 AUC ratios (NS).	Authors' conclusion: 'Severe toxicity was not increased in pediatric patients with the 7/7 genotype when treated with a low-dose protracted schedule of irinotecan. Therefore, UGT1A1 genotyping is not a useful prognostic indicator of severe toxicity for patients treated with this irinotecan dosage and schedule.'

ref. 22 Côté JF et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res 2007;13:3269-75.	3 *28/*28: E *1/*28: E	Prospective study, 89 patients, 8x *28/*28, 44x *1/*28, 37x *1/*1, received irinotecan 180 mg/m^2 every two weeks for twelve cycles in FOLFIRI[a] regimen. *clinical endpoints* *28/*28 versus *1/*1: - Increased incidence of grade 3-4 haematological toxicity by 209% (NS; from 16.2% to 50%). *28/28 versus *1/*28 versus *1/*1: - Increased incidence of grade 3-4 haematological toxicity (NS; 50% versus 25% versus 16.2%). - Increased incidence of grade 3-4 neutropenia (S; 50% versus 23% versus 13.5%). - No significant differences in the incidence of grade 3-4 gastrointestinal toxicity. - No differences in median dose. - Increased incidence of disease-free survival at 3 years (NS; 87% versus 52% versus 42%).	Authors' conclusion: 'This study supports the clinical utility of identification of UGT1A1 promoter polymorphisms before LV5FU2 + CPT-11 treatment to predict early hematologic toxicity. The -3156G>A polymorphism seems to be a better predictor than the UGT1A1 (TA)6TAA>(TA)7TAA polymorphism.'
ref. 23 Ramchandani RP et al. The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. J Clin Pharmacol 2007;47:78-86.	3 *28/*28: E *1/*28: A	Pooled analysis of the data from Innocenti et al. and Iyer et al., 81 patients, 10x *28/*28, 32x *1/*28, 39x *1/*1, received irinotecan 300 or 350 mg/m^2 every three weeks. Toxicity data from the 1st cycle were analysed. *clinical endpoints* - A higher SN-38 AUC and the *28/*28 genotype were significantly associated with lower trough neutrophil counts (S). They both had significantly independent effects on trough neutrophil counts and together accounted for 49% of the variation. A model including the *28 allele only accounted for 22% of the variation. - An alternative model showed that elevated bilirubin levels before treatment and the *28/*28 genotype showed significant associations with lower trough neutrophil counts (S). Together they accounted for 31% of the variation. *kinetic endpoints* - Increased dose-corrected SN-38 AUC for both *1/*28 and *28/*28 versus *1/*1 (S). The genotypes accounted for approximately 10% of the variation in SN-38 AUC.	Authors' conclusion: 'This model can be used to predict the magnitude of decrease in absolute neutrophil count, which can guide safer dosing regimens of irinotecan. However, we believe that the model could be further refined to have greater predictive power and better clinical utility.'
ref. 24 Zárate Romero R et al. Potential application of GSTT1-null genotype in predicting toxicity associated to 5-fluouracil irinotecan and leucovorin regimen in advanced stage colorectal cancer patients. Oncol Rep 2006;16:497-503.	3 *1/*28: AA	51 patients, 26x *1/*28, 21x *1/*1, received irinotecan 180 mg/m^2 every two weeks in combination with 5-fluorouracil and folinic acid for a median five cycles. *clinical endpoints* - No association of the *28 allele with grade 3 haematological toxicity (NS). - No association of the *28 allele with grade 3 gastrointestinal toxicity (NS). Grade 4 toxicity was not found in this study, 78% of the grade 3 toxicity concerned gastrointestinal toxicity.	Authors' conclusion: 'Patients with the UGT1A1*28 allele may develop toxicity easily after irinotecan chemotherapy. In our treatment schedule, this relation was not observed.'
ref. 25 de Jong FA et al. Prophylaxis of irinotecan-induced diarrhea with	3	Prospective study, 52 patients, 3x *28/*28, 23x *1/*28, 26x *1/*1, received irinotecan 350 mg/m^2 every three weeks in combination with neomycin or placebo. Pharmacokinetic parameters were determined for 43 patients, 2x *28/*28, 19x *1/*28, 21x *1/*1. Relevant foods and CYP3A inhibitors or	Authors' conclusion: 'It is suggested that the UGT1A1*28 genotype status could be used as a

neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11:944-54. **ref. 25, continuation**	(*28/*28 + *1/*28): D	inducers were excluded, apart from prophylactic anti-emetics. Neomycin did not affect irinotecan toxicity or pharmacokinetics. *clinical endpoints* (*28/*28 + *1/*28) versus *1/*1: - The incidence of grade 2-3 diarrhoea increased by 100% (S; from 34.6% to 69.2%). - The incidence of grade 0-1 diarrhoea decreased by 53% (S; from 65.4% to 30.8%). - No difference in the incidence of grade 3-4 neutropenia (NS). - No significant decrease in trough neutrophil counts (NS). *kinetic endpoints* *1/*1 versus *28/*1 versus *28/*28: - Decreased median SN-38 metabolic clearance (S; from 1268 to 804 to 489 L/h).	screening tool for a priori prevention of irinotecan-induced delayed-type diarrhea.' SN-38 clearance versus *1/*1: *1/*28: 63% *28/*28: 39% SN-38 clearance versus all genotypes: *1/*28: 79% *28/*28: 48%
ref. 26 Toffoli G et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2006;24:3061-8.	3 *28/*28: E *28/*28: AA[#] *1/*28: A	Prospective study, 250 patients, 22x *28/*28, 114x *1/*28, 114x *1/*1, irinotecan 180 mg/m^2 every two weeks in FOLFIRI[a] regimen, other co-medication not known; *clinical endpoints* - 1st cycle: significant association between *28 allele and grade 3-4 haematological toxicity, no association with non-haematological toxicity (including diarrhoea). - Entire treatment (dose adjusted to adverse events): no association between *28 allele and toxicity or dose reduction. - *28/*28: During 1st cycle: OR severe haematological toxicity versus *1/*1 was 8.63 (95% CI 1.31-56.55), non-haematological toxicity OR = 4.10 (95% CI 0.86-19.55). Throughout entire treatment: haematological toxicity OR = 1.97 (95% CI 0.56-6.99), non-haematological toxicity OR = 1.41 (95% CI 0.45-4.47). No significant difference in dose reduction versus *1/*1 (from 17.5% to 18.2%). Significant decrease in the risk of progressive/stable disease and progression versus *1/*1, OR = 0.32 (95% CI 0.12-0.86) and 0.19 (95% CI 0.04-0.89) respectively. There was no significant increase in overall survival. - *1/*28: During 1st cycle: OR severe haematological toxicity versus *1/*1 was 3.47 (95% CI 0.69-17.34), non-haematological toxicity OR = 0.63 (95% CI 0.15-2.75). Throughout entire treatment: haematological toxicity OR = 1.93 (95% CI 0.89-4.23), non-haematological toxicity OR = 1.09 (95% CI 0.53-2.24). The incidence of dose reduction increased from 17.5% to 23.2% versus *1/*1 (NS by 33%). The risk of progressive/stable disease and progression decreased non-significantly versus *1/*1, OR = 0.92 (95% CI 0.53-1.56) and 0.77 (95% CI 0.42-1.39) respectively. *kinetic endpoints* Significant correlation between the *28 allele and a lower SN-38G/SN-38 AUC ratio or a higher irinotecan AUC x (SN-38/SN-38G). These kinetic parameters also significantly differ between the group with and the group without serious toxicity. N.B.: 5-FU dosed individually guided by adverse events.	Authors' conclusion: 'The results indicate that UGT1A1*28 polymorphism is of some relevance to toxicity; however, it is less important than discussed in previous smaller trials. In particular, the possibility of a dose reduction for irinotecan in patients with a UGT1A1*28 polymorphism is not supported by the result of this analysis.' 'The observed increased response rate in patients with lower GR and increased BI (indicative of a biochemical effect of a reduced UGT enzyme activity) and the trend towards increased tumor response and survival in *28/*28 patients suggest the need for careful consideration before irinotecan dose reduction in patients carrying the polymorphic *28 allele is recommended.'
ref. 27 Han JY et al. Comprehensive analysis of	3	81 patients, irinotecan 80 mg/m^2 on day 1 (+cisplatin) and day 8 of 3-weekly cycles, other co-medication not known; *28:	

UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol 2006;24:2237-44. **ref. 27, continuation**	*1/*28: AA *1/*6: A *6/*6: E	Genotyping: 12x *28/*1, 69x *1/*1 *kinetic endpoints* - *28/*1: SN-38G/SN-38 AUC ratio versus *1/*1 **increased** from 10.9 to 14.9 (NS by 37%). *clinical endpoints* - *28/*1: no differences in tumour response, toxicity or dose versus *1/*1. *6: Genotyping: 6x *6/*6, 26x *1/*6, 49x *1/*1 *kinetic endpoints* - *6/*6: SN-38 AUC increased from 113.9 to 200.4 ng.hour/mL versus *1/*1 (S by 76%). - *1/*6: SN-38 AUC increased from 113.9 to 126.7 ng.hour/mL versus *1/*1 (S by 11%). - *6/*6 : no difference in the weekly irinotecan dose (in mg/m^2/week) versus (*1/*6+*1/*1) (NS) *clinical endpoints (*6/*6 versus (*1/*6+*1/*1))* - The percentage of responders decreased from 50% to 0% (S) - Decreased progression-free survival (S) and overall survival (S) - The percentage of patients with grade 4 neutropenia increased from 24% to 67% (S by a factor 2.8) - No difference in the percentage of patients with grade 3 diarrhoea (NS)	
ref. 28 McLeod HL et al. UGT1A1*28, toxicity and outcome in advanced colorectal cancer: results from Trial N9741. J Clin Oncol 2006;24 (suppl. abstr. 3520).	3 *28/*28: E *1/*28: E	520 patients, 212 received irinotecan 100-125 mg/m^2 once weekly, 109x in IFL[a] regimen (11x *28/*28, 54x *1/*28, 44x *1/*1), 103x in IROX[b] regimen, other co-medication not known; - *28/*28: the incidence of grade 4 neutropenia with IROX regimen increased significantly from 9.6% to 54.5% versus *1/*1 (S by 468% and OR 15.3, 95% CI 3-78); this increase was non-significant with the IFL regimen (from 6.8% to 18.2%, NS by 168%). - *1/*28: the incidence of grade 4 neutropenia with IROX regimen increased significantly from 9.6% to 15.0% versus *1/*1 (S by 56%); this increase was non-significant with the IFL regimen (from 6.8% to 11.1%, NS by 63%). UGT1A1 is not a predictor of incidence of diarrhoea, tumour response, time to progression or overall survival.	
ref. 29 Massacesi C et al. Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. Cancer 2006;106:1007-16.	3 *28/*28: E *1/*28: F	56 patients, 7x *28/*28, 22x *1/*28, 27x *1/*1, irinotecan 80 mg/m^2 weekly and raltitrexed every three weeks, other co-medication not known; - *28/*28 + *1/*28: significant increase versus *1/*1 in the incidence of diarrhoea, nausea and fatigue, no increase in neutropenia and liver toxicity. Genotype has **no** predictive power for response, time to disease progression or overall survival. - A patient with the *1/*28 genotype died of kidney failure due to severe diarrhoea and vomiting in combination with haematological toxicity.	

ref. 30 Wright MA et al. A phase I pharmacologic and pharmacogenetic trial of sequential 24-hour infusion of irinotecan followed by leucovorin and a 48-hour infusion of fluorouracil in adult patients with solid tumors. Clin Cancer Res 2005;11:4144-50.	3 *28/*37: A *1/*28: A	32 patients, 30x genotyped, 3x *28/*37,18x *1/*28, 9x *1/*1, irinotecan 70-140 mg/m^2 every two weeks, folinic acid and 5-FU, other co-medication not known; - *28/*37 + *1/*28: significantly increased SN-38/SN-38G AUC ratio versus *1/*1.	
ref. 31 Kweekel DM et al. Ondersteuning van de chemotherapiekeuze [Support for choice of chemotherapy]. Pharm Weekblad 2005;20:685-7.	3 *28/*28: D *1/*28: D	8 patients, 1x *28/*28, 2x *1/*28, 5x *1/*1, irinotecan+capecitabine doses not known, other co-medication not known; - *28/*28: no response, ≥ grade 3 toxicity. - *1/*28: 1 patient responded while another did not. Both < grade 3 toxicity. - *1/*1: response in 3 in 5 patients, 1 patient had ≥ grade 3 toxicity, other 4 < grade 3.	Subpopulation of the CAIRO study by Dutch Colorectal Cancer Group.
ref. 32 Steiner M et al. 5-fluorouracil/ irinotecan induced lethal toxicity as a result of a combined pharmacogenetic syndrome: report of a case. J Clin Pathol 2005;58:553-5.	1 *1/*28: F	Female patient received irinotecan 80 mg/m^2 weekly + 5-FU, folinic acid. The dose was reduced due to adverse events (grade 2 nausea, grade 1 leukopenia) after the second cycle. Severe diarrhoea and grade 4 neutropenia occurred. The patient developed sepsis and died. Genotyping: *1/*28 and heterozygous DPD*2A.	
ref. 33 Soepenberg O et al. Phase I pharmacokinetic, food effect, and pharmacogenetic study of oral irinotecan given as semisolid matrix capsules in patients with solid tumors. Clin Cancer Res 2005;11:1504-11.	3 *28/*28: A *1/*28: A	25 patients of which 23 were genotyped, 1x *28/*28, 8x *1/*28, 13x *1/*1, 1x *36/*1, oral irinotecan 70-80 mg/m^2 on days 1 to 5 of three-weekly cycles, co-medication not known; *28 allele had a significant effect on SN-38 Cmax. No difference in toxicity.	
ref. 34 Zhou Q et al. Pharmacogenetic profiling across the irinotecan pathway in Asian patients with cancer.	3 *28/*28: AA *1/*28: AA	29 patients, 11% *28, oral irinotecan 100 mg/m^2 weekly, co-medication not known; The UGT1A1 genotype did not have a significant effect on kinetic parameters of irinotecan, SN-38 or SN-38G.	

Br J Clin Pharmacol 2005;59:415-24.		N.B.: No genotyping was performed for the *6 allele, which is common among Asian populations.	
ref. 35 Carlini LE et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin Cancer Res 2005;11:1226-36.	3 *28/*28: AA *28/*37: AA	67 patients, 1x *36/*1, 1x *36/*37, 28x *1/*1, 29x *1/*28, 1x *1/*37, 5x *28/*28, 1x *28/*37, irinotecan 100-125 mg/m^2 + capecitabine on days 1 and 8 of three-weekly cycles, other co-medication not known; - No significant association between genotype and tumour response, but there was a trend towards a better response in patients with low enzyme activity (*28/*28 and *28/*37) compared to those with high enzyme activity (*36/*1 and *1/*1), by 83% and 46% respectively. - No significant association between genotype and toxicity, none of the six patients with low enzyme activity had toxic adverse events.	
ref. 36 Kitagawa C et al. Genetic polymorphism in the phenobarbital-responsive enhancer module of the UDP-glucuronosyltransferase 1A1 gene and irinotecan toxicity. Pharmacogenet Genomics 2005;15:35-41.	3 *28/*28: E	119 patients, 7x *28/*28, 17x *1/*28, 95x *1/*1, irinotecan dose not known, co-medication not known; - *28/*28: significant association between genotype and the occurrence of severe toxicity, leukopenia and/or diarrhoea (OR 5.33, 95% CI 2.02-14.1). N.B.: No genotyping was performed for the *6 allele, which is common among Asian populations.	
ref. 37 Marcuello E et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 2004;91:678-82.	3 *28/*28: E *1/*28: E	95 patients 10x *28/*28, 45x *1/*28, 40x *1/*1, one of the following four regimens: irinotecan 350 mg/m^2 every three weeks, irinotecan 350 mg/m^2 every three weeks + raltitrexed, irinotecan 80 mg/m^2 once weekly + 5-FU, irinotecan 180 mg/m^2 every two weeks + 5-FU+levofolinic acid, other co-medication not known; - *28/*28: significant increase versus *1/*1 in the incidence of diarrhoea [from 17% to 70% (S by 312%)] and asthenia [from 25% to 70% (S by 180%)]. Non-significant increase in grade 3-4 haematological toxicity from 15% to 40% (NS by 167%). UGT1A1 genotype is the only variable associated with severe diarrhoea. No difference in overall survival. - *1/*28: significant increase versus *1/*1 in the incidence of diarrhoea [from 17% to 33% (S by 94%)] and asthenia [from 25% to 38% (S by 52%)]. Non-significant increase in grade 3-4 haematological toxicity from 15% to 27% (NS by 80%). No difference in overall survival.	
ref. 38 Rouits E et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. Clin Cancer Res 2004;10:5151-9.	3 *1/*28: E	75 patients, 7x *28/*28, 35x *1/*28, 31x *1/*1, 2x *36/*1 or *36/*28, irinotecan 85 mg/m^2 weekly + 5-FU + folinic acid or irinotecan 180 mg/m^2 every two weeks in FOLFIRI[a] regimen, other co-medication not known; - *28/*28: grade 3-4 neutropenia increased from 10% to 71% (S by 638%), grade 4 diarrhoea increased from 3% to 29% (NS by 793%). - *1/*28: grade 3-4 neutropenia increased from 10% to 40% (S by 313%), grade 4 diarrhoea increased from 3% to 6% (NS by 79%).	

ref. 38, continuation	*28/*28: F (2)	One patient (*28/*28), who developed grade 4 diarrhoea with dehydration, fever and collapse, died. N.B.: 5-FU dosed individually guided by adverse events.	
ref. 39 Paoluzzi L et al. Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. J Clin Pharmacol 2004;44:854-60.	3 *28/*28: A *1/*28: A	94 patients, 86x genotyped: 5x *28/*28, 37x *1/*28, 44x *1/*1, median irinotecan dose 600 mg, no relevant co-medication; *kinetic endpoints* - *28/*28: SN-38G/SN-38 AUC ratio decreased from 7.00 to 2.51 versus *1/*1 (S by 64%). SN-38 AUC increased (S by 18%; from 508 to 600 ng.h/mL). No significant differences in irinotecan and SN-38G AUCs. - *1/*28: SN-38G/SN-38 AUC ratio decreased from 7.00 to 6.26 versus *1/*1 (S by 11%). SN-38 AUC increased (S by 18%; from 508 to 600 ng.h/mL). Other parameters differed NS from *1/*1. *clinical endpoints* There was no significant association between the UGT1A1*28 genotype and the occurrence of grade 2-4 diarrhoea.	SN-38 AUC versus *1/*1: *1/*28: 118% *28/*28: 118% SN-38 AUC versus all genotypes: *1/*28: 109% *28/*28: 109%
ref. 40 Sai K et al. UGT1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. Clin Pharmacol Ther 2004;75:501-15.	3 *28/*28: A *1/*28: A *6: A	195 patients, 85 with cancer, single dose of irinotecan 60-150 mg/m^2, other oncolytic drugs as co-medication. *28: Genotyping: 3x *28/*28, 15x *1/*28, 23x *1/*1. - *28/*28: SN-38G/SN-38 AUC ratio decreased from 6.36 to 3.57 versus *1/*1 (S by 44%). - *28/*1: SN-38G/SN-38 AUC ratio decreased from 6.36 to 3.45 versus *1/*1 (S by 46%). - *28 haplotype had the greatest impact on AUC ratio. *6: Genotyping: 2x *6/*6, 14x *1/*6, 23x *1/*1. - *6/*6: SN-38G/SN-38 AUC ratio decreased from 6.36 to 4.27 versus *1/*1 (trend, NS by 33%). - *6/*1: SN-38G/SN-38 AUC ratio decreased from 6.36 to 4.23 versus *1/*1 (NS by 33%). - *6/*60: SN-38G/SN-38 AUC ratio decreased versus *1/*60 (trend, NS by 33%). - Significant association of *6 with decrease in SN-38G/SN-38 AUC in multiple regression analysis. NOTE: the factors gender, co-medication, irinotecan dose, tumour type and performance status did not affect the AUC ratio. Age did.	
ref. 41 Innocenti F et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22:1382-8.	3 *28/*28: E *1/*28: E	65 patients, 6x *28/*28, 25x *1/*28, 30x *1/*1, 2x *1/*37, 1x *36/*1, 1x *28/*37, irinotecan 350 mg/m^2 every three weeks, co-medication not known; *clinical endpoints* - *28/*28: grade 4 neutropenia increased from 0% to 50% versus *1/*1 (S). Grade 3 diarrhoea in 1x *28/*28 versus 0x *1/*1. - *1/*28: grade 4 neutropenia increased from 0% to 12.5% versus *1/*1 (S). Grade 3 diarrhoea in 2x *1/*28 versus 0x *1/*1. *kinetic endpoints* Significant correlation between SN-38 AUC, SN-38G/SN-38 AUC ratio and number of *28 alleles.	Authors' conclusion: 'There is no consistency across different studies on whether the AUC of irinotecan, SN-38, SN-38G, or a combination of these three parameters (the biliary index) is the strongest predictor of either severe neutropenia or diarrhea. Moreover, the safe dose of irinotecan in UGT1A1*28

ref. 41, continuation		SN-38 AUC: 336 versus 458 versus 542 ng.h/mL for *1/*1 versus *1/*28 versus *28/*28.	homozygous patients has not been definitively identified yet, although it is likely to be approximately a 20% dose reduction given the relationship of genotype to SN-38 exposure.' SN-38 AUC versus *1/*1: *1/*28: 136% *28/*28: 161% SN-38 AUC versus (*1/*1 + *1/*28 + *28/*28): *1/*28: 112% *28/*28: 133%
ref. 42 Font A et al. Weekly regimen of irinotecan/docetaxel in previously treated non-small cell lung cancer patients and correlation with uridine diphosphate glucuronosyl-transferase 1A1 (UGT1A1) polymorphism. Invest New Drugs 2003;21:435-43.	3 *28/*28: AA *1/*28: AA	47 patients, 7x *28/*28, 17x *1/*28, 23x *1/*1, irinotecan 70 mg/m^2 weekly + docetaxel, other co-medication not known; - *28/*28 + *1/*28: no difference in grade 3-4 toxicity versus *1/*1 (decreased from 43% to 41%, NS by 5%). Disease control increased from 34% to 54% (NS by 60%), progression-free survival increased by 33% from 3 to 4 months, survival increased by 27% from 8 to 11 months, 1-year survival increased by 95% from 21% to 41%.	Authors' conclusion: 'But we found no differences in toxicity according to UGT1A1 polymorphism. This patient population has been heavily pretreated and therefore could reduce the relevance of the UGT1A1 polymorphism as a genetic predictive marker, as compared to using first-line irinotecan-treated patients.'
ref. 43 Mathijssen RH et al. Irinotecan pathway genotype analysis to predict pharmacokinetics. Clin Cancer Res 2003;9:3246-53.	3 *28/*28: AA *1/*28: AA	65 patients, 2x *28/*28, 19x *1/*28, 32x *1/*1, irinotecan 350 mg/m^2 every three weeks or 200-300 mg/m^2 every three weeks + cisplatin, co-medication not known; No significant differences in kinetic parameters between different UGT1A1*28 genotypes. There was a trend that the SN-38 AUC increases in the presence of allele variants.	
ref. 44 Iyer L et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43-7.	3 *28/*28: A *1/*28: A	20 patients, 4x *28/*28, 7x *1/*28, 9x *1/*1, irinotecan 300 mg/m^2 every three weeks, co-medication not known; *clinical endpoints* Significant correlation between the absolute trough neutrophil count and genotype. Diarrhoea or grade 3-4 neutropenia only in *28/*28 and *1/*28. *kinetic endpoints* - *28/*28: SN-38G/SN-38 AUC ratio decreased from 9.28 to 2.41 versus *1/*1 (S by 74%), SN-38 AUC_{0-24h} increased from 205.13 to 513.37 ng.h/mL (S by 159%). - *1/*28: SN-38G/SN-38 AUC ratio decreased from 9.28 to 4.04 versus *1/*1 (S by 56%), SN-38 AUC_{0-24h} increased	SN-38 AUC versus *1/*1: *1/*28: 141% *28/*28: 259% SN-38 AUC versus all genotypes: *1/*28: 96%

		from 205.13 to 288.61 ng.h/mL (S by 41%).	*28/*28: 177%
ref. 45 Ando Y et al. Polymorphisms of UDP-glucuronosyl-transferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921-6.	3 *28/*28: E *1/*28: E *6/*6: AA *1/*6: AA	Case-control study including 26 cases (≥ grade 3 diarrhoea, ≥ grade 4 neutropenia on irinotecan) and 92 controls, 65% received various doses of weekly irinotecan, various oncolytic drugs as co-medication, other co-medication not known; *28: 15% of the cases were *28/*28, 31% *1/*28, while this was 3% and 11% respectively for the controls. The difference in *28 allele distribution between cases and controls was significant. *28 allele was a significant risk factor for occurrence of severe irinotecan toxicity, OR was 7.23 (95% CI 2.52-22.3). *6: 0% of the cases were *6/*6, 15% *1/*6, while this was 2% and 23% respectively for the controls. The difference in *6 allele distribution between cases and controls was not significant.	
ref. 46 Wasserman E et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049-51.	2 Gilbert's syndrome: E	Two patients (metastatic colon cancer) with Gilbert's syndrome (low UGT1A1 activity) developed severe diarrhoea and neutropenia on treatment with irinotecan; - Patient 1: 10 cycles of irinotecan 150 mg/m^2 + oxaliplatin, serum bilirubin elevation and grade 4 neutropenia during each cycle. Grade 4 diarrhoea only developed during the first cycle. SN-38G/SN-38 AUC ratio was 1.8. - Patient 2: 2 cycles of irinotecan 200 mg/m^2 + oxaliplatin, serum bilirubin elevation and grade 4 neutropenia during each cycle. Grade 4 diarrhoea only developed during the first cycle. SN-38G/SN-38 AUC ratio was 4.2.	
ref. 47 SmPC Campto (irinotecan hydrochloride trihydrate) 23-11-20.	0 *28/*28: E	<u>Pharmacodynamic data</u>: *Patients with Reduced UGT1A1 Activity:* Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan, to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in highly variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1*28 variant. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar syndrome and Gilbert's syndrome) are associated with reduced activity of this enzyme. Data from a meta-analysis indicate that individuals with Crigler-Najjar syndrome (types 1 and 2) or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of haematological toxicity (grade 3 to 4) following administration of irinotecan at moderate or high doses (>150 mg/m^2). A relationship between UGT1A1 genotype and the occurrence of irinotecan-induced diarrhoea was not established. Patients known to be homozygous for UGT1A1*28 should receive the normally indicated irinotecan starting dose. However, these patients should be monitored for haematological toxicities. A reduced irinotecan starting dose should be considered for patients who have experienced haematological toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on a patient's tolerance of the treatment. There are at present insufficient data to conclude on clinical utility of UGT1A1 genotyping.	

ref. 48 SmPC Campto-sar (irinotecan) 30-01-20 (USA).	0 *28/*28:E	Dosage in patients with reduced UGT1A1 Activity: When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of Camptosar should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment. Warning: Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of Camptosar treatment. In a study of 66 patients who received single-agent Campto-sar (350 mg/m2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype). In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with Camptosar (180 mg/m2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele. In another study in which 109 patients were treated with Camptosar (100–125 mg/m2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homo-zygous for the wild-type allele. When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of Camptosar should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment. A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes. Pharmacokinetics: UGT1A1 activity is reduced in individuals with genetic poly-morphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype).	

[a] FOLFIRI, IFL = irinotecan, fluorouracil and leucovorin (= folinic acid)
[b] IROX = irinotecan, oxaliplatin
AA[#]: there was a significant effect, but this effect was positive instead of negative.

Risk group	*28/*28 and PM with UGT1A1 inhibitors (e.g. ketoconazole, atazanavir, gemfibrozil, indinavir)

Comments:

- KNMP comment: on theoretical grounds, the recommendation for the IM and PM phenotypes is the same as the recommendation for *1/*28 and *28/*28 respectively. The SN-38 glucuronide/SN-38 AUCs are almost the same for *28/*28 and *6/*6, suggestive of a similar effect on irinotecan metabolism (Minami H et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics. 2007;17:497–504).
- Administration of irinotecan was *intravenous* unless stated otherwise.
- Given the large number of articles, the only articles included after July 2006 (Toffoli et al.) were those that included greater or equal than 25 patients with one or more *28 alleles.
  The only clinical studies included for the period 2008-2017 were meta-analyses. From 2008 to 2014 only meta-analyses with mainly Caucasian patients were included. Three Asian meta-analyses investigating the effect of *6 and *28 were not included as these are insufficiently relevant to the situation in the Netherlands. Individual studies were not included as large studies (n > 200) including mainly Caucasian patients were already included in one of the recent meta-analyses. From 2014, meta-analyses were included if the effect of *28 was analysed, either alone or in combination with *6. Individual studies were not included, because they did not add enough to the evidence. For the period after 2017, clinical studies were only included if they investigated more than 500 patients with the additional requirements of more than 150 cases for case-control studies and analysis of the effect of *28 in the case of meta-analyses. Kinetic studies were only included if exposure to or clearance of SN-38 was determined for the *1/*1, *1/*28 and *28/*28 genotypes and if these were the most important genotypes investigated within the population (i.e. studies among Caucasians) (for the period from 2008 to 2014) or for the *1/*1, *1/*28 and/or *1/*6, and *28/*28 and/or *6/*28 and/or *28/*28 genotypes (for the period from 2014). For the periods from 2008 to 2014 and after 2017, there were no relevant studies investigating the effect of dose adjustments. This means that there were no studies that investigated the effect of approximately 30% lower initial doses for PM compared to the standard dose for NM and IM in this period.
- <u>Existing guidelines</u>:
  - 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 homozygotes a dose reduction of 30% is recommended.
- <u>Cost-effectiveness</u>
  - Henderson R et al. Molecular biomarkers and precision medicine in colorectal cancer: a systematic review of health economic analyses. Oncotarget 2019;10:3408-23. PMID: 31164962.
    The authors performed a systematic review of cost effectiveness analyses and concluded that current research does not support UGT1A1 polymorphism status as a cost-effective guide to irinotecan dosing. In all studies, additional costs per quality-adjusted life-year (QALY) for UGT1A1 genotyping for guidance of irinotecan dosing were in excess of £1 million (€1 million).
    The authors do not explain how they selected the values for additional costs per QALY gained. Butzke 2016 mentions dose reduction for *28/*28 and *1/*28 to be cost saving, dose reduction for *28/*28 not to be cost-effective with additional costs of € 17,040,017 per QALY gained, and additional costs of € 65 million per QALY gained for administration of a prophylactic granulocyte colony stimulating factor analogue (pegfilgrastim) instead of dose reduction for *28/*28 and *1/*28. The authors of the review indicate that Butzke 2016 calculated additional costs of € 69 million per QALY gained for UGT1A1 genotype guided irinotecan dosing. Gold 2009 mentions that genotyping prior to treatment saves costs, but that results were dependent on the effectiveness of the treatment, such that the therapeutic effectiveness of irinotecan in PM patients after dose reduction would need to be > 98.4% of that of the full dose in order for genetic testing to continue to be the preferred treatment at the limit of US$ 100.000 per quality adjusted life year. The authors of the review indicate that Gold 2009 found another treatment to be both better and cheaper than genotype-guided dosing. Obradovic 2008 concluded that genotyping in combination with a reduced initial irinotecan dose for patients with the *28/*28 genotype was cost-saving among White and African populations. The authors of the review calculated additional costs of € 1.5 million per QALY gained with the data from Obradovic 2008.
    The authors indicate that three of the irinotecan studies (Butzke 2016, Gold 2009, and Obradovic 2008) identified in the systematic review suggest that prior testing for UGT1A1 may be cost saving, but that their systematic review is inconclusive as to whether testing improves patient outcomes, with both positive (Butzke 2016) and negative (Gold 2009) QALYs being reported. Goldstein 2015 stated that they cannot recommend UGT1A1 genotyping to guide irinotecan dosing, and that any dose reduction should be based on clinical parameters, rather than UGT1A1 status (Goldstein DA et al. Costs and effectiveness of genomic testing in the management of colorectal cancer. Oncology (Williston Park) 2015;29:175-83). In addition, they indicate that Lu 2015 attempted a different approach by escalating the dose in UGT1A1 *1/*1 and UGT1A1 *1/*28, with positive therapeutic results without the development of adverse effects, and that a randomised controlled trial of this approach is ongoing (Lu CY et al. Clinical implication of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab combined with FOLFIRI in the first-line setting. Transl Oncol 2015;8:474-79 and Yeh YS et al. Prospective analysis of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab plus FOLFIRI as the first-line setting: study protocol for a randomized controlled trial. Trials 2016;17:46). As the optimum dosing of irinotecan based on UGT1A1 status has yet to be defined (Semrad TJ, Kim EJ. Molecular testing to optimize

therapeutic decision making in advanced colorectal cancer. J Gastrointest Oncol 2016;7:S11–20), UGT1A1 genotyping to guide irinotecan dosing will most likely need to be revisited following the availability of results from randomized controlled trials such as the one highlighted above in order to determine its efficacy and cost-effectiveness.

Butzke 2016, Pichereau 2010, Gold 2009, and Obradovic 2008 were included in the systematic review. Two of these studies (Butzke 2016 and Gold 2009) reported the incremental costs per quality adjusted life-year (QALY), one per life-year gained (Obradovic 2008) and one reported the costs to avoid 1 case of febrile neutropenia (Pichereau 2010). The cost-effectiveness analysis was described from the perspective of the healthcare payer in 3 studies (Butzke 2016, Gold 2009, and Obradovic 2008), whereas Pichereau 2010 focussed on the perspective of the hospital. While Butzke 2016 employed a decision analytic approach in combination with a Markov model and a lifetime time horizon, the remaining 3 studies solely employed a decision tree to model treatment strategies, with no specified time horizon (Pichereau 2010, Gold 2009, and Obradovic 2008). 2 of the studies employed a discount rate of 3% (Butzke 2016 and Gold 2009). These studies also employed a health utility questionnaire; EQ-5D was used by Butzke 2016, while Gold 2009 did not specify which health utility questionnaires they employed. 3 of the studies reported willingness-to-pay thresholds, which ranged from €50,000 in 2013 (£46,950 or €53,340 in 2016) (Butzke 2016) to US$100,000 in 2006 (£81,606 or €92,713 in 2016) (Pichereau 2010 and Obradovic 2008). Gold 2009 and Butzke 2016 performed both a deterministic sensitivity analysis (testing parameters such as clinical effects, disease progression, QALYs and costs one at a time) and a probabilistic sensitivity analysis (testing parameters such as clinical effects, disease progression, QALYs and costs in combination), whereas Obradovic 2008 and Pichereau 2010 only performed a probabilistic sensitivity analysis. These analyses were employed to address the uncertainty surrounding the cost-effectiveness of irinotecan dosing based on the UGT1A1 genotyping.

- Wei X et al. Cost-effectiveness analysis of UGT1A1*6/*28 genotyping for preventing FOLFIRI-induced severe neutropenia in Chinese colorectal cancer patients. Pharmacogenomics 2019;20:241-9. PMID: 30628534.

The authors concluded that UGT1A1*6/*28 genotyping was cost saving for Chinese metastatic colorectal cancer patients. Genotyping with dose reduction (50% reduction in irinotecan dose for *28/*28 and PM, standard dose for the other genotypes) was both cheaper and better than either no genotyping or genotyping without dose adjustment. Compared with no genotyping and genotyping with unchanged dose, it resulted in only marginal quality-adjusted life-year increases (0.0011 and 0.0012) but a cost reduction of $651.12 and $805.22 per patient, respectively. It could lead to an absolute decrease in the incidence of severe neutropenia to 40.25 cases including 0.01 deaths per 1000 exposures. One-way sensitivity analyses revealed that the model was relatively robust. Only the probability of severe neutropenia in wild-type and heterozygote with full irinotecan dose, and the probability of severe neutropenia with full dose without genotyping had a considerable effect on the net benefit of genotyping and dose reduction versus no genotyping. The prevalence of patients with two variant alleles (*28/*28 or PM) was the same in this Chinese population as in the Netherlands (9%).

Remarks:

- Calculations were made from the perspective of the Chinese healthcare system.
- Only the adverse event neutropenia was modelled, only neutropenia grade 4 was considered severe neutropenia.
- Only direct medical costs were included in the calculation.
- The strategy ‘genotyping and dose reduction’ resulted in costs of US$ 30,432.37, in 0.3883 QALYs, and in 40.25 cases of neutropenia grade 4 per 1000 patients. The strategy ‘no genotyping’ resulted in costs of US$ 31,083.49, in 0.3872 QALYs, and in 51.6 cases of neutropenia grade 4 per 1000 patients.

Assumptions/data used:

- Treatment of patients with FOLFIRI (irinotecan in combination with 5-fluorouracil and folinic acid) for 12 weeks.
- It was assumed that all strategies would not affect the average life expectancy - this was consistent with clinical evidence from the prospective, nationwide, multicentre, clinical trial of Qin 2017 that there were no significant differences of progression-free survival and overall survival among the patients with dose reduction or no dose reduction (Qin S. Impact of irinotecan dose adjustment based on UGT1A1 genotype on the toxicity and efficacy of FOLFIRI regimen in treating patients with metastatic colorectal cancer: a prospective study [Master’s Degree Thesis]. The Medical University Of Anhui, Anhui, China (2017)).
- It was also assumed that the FOLFIRI regimen had 100% efficacy in all patients and the same efficacy at a reduced dose regardless of the genotype because homozygotes exhibit slower glucuronidation and a higher plasma concentration of SN-38.
- Severe neutropenic status was assumed to last 1 week, and the death from severe neutropenia was assumed at the end of every chemotherapy cycle (lasting 2 weeks).
- The willingness to pay threshold was $26,508 (3 times the domestic Gross Domestic Product per capita).

Most parameters in the decision tree were based on the literature (mainly the prospective, nationwide, multicentre, clinical trial of Qin 2017 (Qin S. Impact of irinotecan dose adjustment based on UGT1A1 genotype on the toxicity and efficacy of FOLFIRI regimen in treating patients with metastatic colorectal cancer: a prospective study [Master’s Degree Thesis]. The Medical University Of Anhui, Anhui, China (2017)):

- the prevalence of patients with two variant alleles was 9% (as is the case in the Netherlands)
- the probabilities of each of the genotypes and all genotypes together developing neutropenia grade 4 (for patients with two variant alleles both on full and reduced irinotecan dose) were derived from Qin 2017, Wen

2014 and Wang 2012 (Wen F et al. Cost–effectiveness analysis of colon cancer treatments from MOSIAC and No. 16968 trials. World J Gastroenterol 2014;20:17976-84 and Wang Y et al. Correlation between UGT1A1 gene polymorphisms and toxicity and efficacy in patients with metastatic colorectal cancer treated with irinotecan based chemotherapy. Chinese Clinical Oncol 2012;17:961-6)
- the probability of death from neutropenia grade 4 was derived from Gold 2009
- quality-of-life weights (utility values) associated with metastatic colorectal cancer and severe neutropenia were derived from literature
- the cost of full dose FOLFIRI was US$ 1016.18, and the cost of FOLFIRI with 50% dose of irinotecan US$ 560.87
- the cost of one UGT1A1 test was US$ 142.12
- the costs for neutropenia grade 0-3 and neutropenia grade 4 were US$ 388.17 and US$ 2044.12, respectively
- the cost of routine examination and testing was US$ 349.98.

- Butzke B et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. Acta Oncol 2016;55:318-28. PubMed PMID: 26098842.

The authors concluded that this model-based synthesis of the most recent evidence suggests that pharmacogenetic UGT1A1 testing prior to irinotecan-based chemotherapy is both cheaper and better than non-personalized colon cancer care in Germany. UGT1A1 genotyping of German patients with metastatic colorectal cancer before initiation of irinotecan and reducing the dose with 25% for *1/*28 and *28/*28 was cost-saving compared to no genotyping (only marginally increased quality-adjusted life years (QALY) (increase with 0.0002), but a cost reduction of € 580 per patient). In the probabilistic analysis, genotyping and dose reduction was the optimal strategy in approximately 100% of simulations at a threshold of € 50,000 per QALY. Deterministic sensitivity analysis shows that uncertainty for this strategy originated primarily from costs for irinotecan-based chemotherapy, from the prevalence of neutropenia among heterozygous patients, and from whether dose reduction is applied to both homozygotes and heterozygotes or only to the former. If dose reduction is only applied to homozygotes, the strategy increased costs compared to no testing by about € 99 and resulted in a QALY gain of less than 0.0001. Compared to the no testing strategy this scenario would result in additional costs of € 17,040,017 per QALY gained and thus would not be cost effective.

Administration of a prophylactic granulocyte colony stimulating factor analogue (pegfilgrastim) for homozygous and heterozygous patients instead of dose reduction resulted in the same health gains but increased costs by € 10,773, resulting in additional costs of € 65 million per QALY gained.

Remarks:
- Calculations were made from the perspective of the German statutory health insurance and with a life time horizon.
- The strategy ‘genetic test and dose reduction’ resulted in costs of € 23,414 and in approximately 1.1292 QALYs, the strategy ‘no genetic test’ in costs of € 23,995 and in 1.1290 QALYs, and the strategy ‘genetic test and growth factors’ in costs of € 34,187 and in 1.1292 QALYs.

Assumptions/data used:
- Treatment of patients with FOLFIRI (irinotecan in combination with 5-fluorouracil and folinic acid).
- The UGT1A1 genotype can predict individuals’ risks to develop sever neutropenia and diarrhoea.
- Patients with severe neutropenia/diarrhea have a reduction in quality of life which lasts for one week.
- Dose-reduction and the administration of growth factors are not assumed to affect the effectiveness of the irinotecan treatment.
- Irinotecan treatment is limited to a maximum of 26 weeks.
- After the occurrence of severe side-effects an alternative chemotherapy regime is administered.
- The duration of the subsequent therapy line was limited to a maximum of 24 weeks.
- The subsequent line of therapy is only assumed to influence costs but it does not affect overall survival and quality of life. This indicates that the subsequent therapy after severe neutropenia was assumed to completely prevent further cases of neutropenia.
- Most parameters in the decision tree were based on the literature:
  - the frequency of the *28 allele was 31%
  - the probabilities of each of the genotypes developing severe neutropenia or severe diarrhoea were derived from Coté 2007 and Martinez-Balibrea 2010 respectively
  - the probability of hospitalization due to neutropenia or diarrhoea was 0.421 (literature, probability of febrile neutropenia) and 0.25 (expert opinion) respectively
  - the probability of death from hospitalized neutropenia or diarrhoea was 0
  - the risk ratios for severe neutropenia and severe diarrhoea upon dose reduction were 0.299 and 0.329 respectively (Toffoli 2010)
  - the costs of full dose FOLFIRI were € 1,211.85 per chemotherapy cycle, the costs of subsequent chemotherapy were € 1,061.14 per chemotherapy cycle, the lump sum costs for chemotherapy were € 145 quarterly
  - the costs of one UGT1A1 test were € 69.90
  - the costs for hospitalization for severe neutropenia or severe diarrhoea followed by recovery were € 3,227.93 and € 1,528.05 per case respectively, the costs of dying in the hospital due to an adverse event was € 11,748.79 per case

- the costs of physician office visits for neutropenia or diarrhoea were € 628.36 and € 39.03 per case respectively

- Pichereau S et al. Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer. J Pharm Pharm Sci 2010;13:615-25. PubMed PMID: 21486535.
  The authors concluded that UGT1A1 genotyping at the hospital before initiation of irinotecan is cost-effective. Genotyping and prophylactic administration of granulocyte colony stimulating factor (filgrastim or lenograstim) to *28/*28 patients enables prevention of 91 cases of febrile neutropenia per 1000 patients at an acceptable cost (€ 942.80-1090.10 per case). The costs of neutropenia-related hospitalisation are estimated at € 1448.90-4126.90 per case.
  Remarks:
  - The assumptions used for the risk of febrile neutropenia differed between both strategies. Without the use of granulocyte colony stimulating factor, the non-genotyping strategy used an overall risk of 6.4% and the genotyping strategy an overall risk of 16.5% (0% for NM; 14.3% for IM and 100% for PM). This underestimates the costs of the non-genotyping strategy. This is offset by an underestimate of the costs of the genotyping strategy because the costs of the granulocyte colony stimulating factor are not included.

  Assumptions/data used:
  - Treatment of patients with FOLFIRI (irinotecan 180 mg/m^2 once every two weeks in combination with fluorouracil and folinic acid) for metastatic colorectal cancer.
  - Parameters in the decision tree were based on the literature (genotype frequency and occurrence of neutropenia on irinotecan therapy) and on medical practice in France
  - Dose reduction by 25% on occurrence of grade III-IV neutropenia and possibly delayed next cycle
  - Need for hospitalisation and switch to another non-irinotecan-based regimen on development of febrile neutropenia
  - *28/*28 received prophylactic granulocyte colony stimulating factor and did not develop neutropenia, *1/*1 and *1/*28 received the same treatment as non-genotyped patients
  - Neutropenia occurred most commonly in the first cycle of chemotherapy
  - Costs of genotyping (actual costs), chemotherapy in day hospital (only differed for the second cycle, oncolytic drugs for patients with body surface area of 1.85 m^2) and hospital treatment for febrile neutropenia were included; the costs of granulocyte colony stimulating factor were not, as these were paid for by the public pharmacy.

- Gold HT et al. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyl transferase 1A1 before irinotecan administration for metastatic colorectal cancer. Cancer 2009;115:3858-67. PubMed PMID: 19517472.
  The authors concluded that genotyping prior to treatment costs less (saving US$ 272 per tested patient) and slightly improves the quality of life (by 0,073 quality adjusted day per tested patient). The results were dependent on the effectiveness of the treatment, but not on the assumptions on the risk of adverse events. Testing 10,000 patients would prevent 84 cases of severe neutropenia, including 4.5 deaths. At the limit of US$ 100.000 per quality adjusted life year, the therapeutic effectiveness of irinotecan in PM patients after dose reduction would need to be ≥ 98.4% of that of the full dose in order for genetic testing to continue to be the preferred treatment.
  KNMP comment: Recent meta-analyses have not shown differences in the effectiveness of the treatment between PM and NM patients on the full dose. As PM patients do not benefit from the higher exposure to the active metabolite SN-38 at the full dose, it is unlikely that the effectiveness of the treatment decreases on dose reduction that would make the exposure equal to that of NM patients receiving the full dose.
  Assumptions/data used:
  - Treatment of patients with FOLFIRI (irinotecan 175 mg/m^2 once every two weeks in combination with fluorouracil and folinic acid) for metastatic colorectal cancer
  - Parameters were based on the literature and product specifications (test performance, occurrence of grade 3-4 neutropenia at the full dose and after a 25% dose reduction and contribution to quality of life)
  - Irinotecan dose reduction by 25% for *28/*28 patients and full dose for the remaining patients
  - Hospitalisation of 23% of the patients with grade 3-4 neutropenia and death of 0.1% of these patients
  - Life expectancy of 24 months after FOLFIRI
  - Costs were based on health insurance cover (Medicare) for genotyping, hospitalisation for febrile neutropenia, doctor's visits and FOLFIRI chemotherapy

- Obradovic M et al. Pharmacogenomics 2008;9:539-49 investigated the cost-effectiveness of UGT1A1-genotyping in second-line, high-dose, three-weekly irinotecan monotherapy in colon cancer.
  The authors concluded that genotyping in combination with a reduced initial irinotecan dose for patients with the *28/*28 genotype was cost-saving among Caucasian and African populations. They also concluded that a three-weekly high-dose treatment regimen dosed 20% lower cost less and was more patient-friendly than a weekly low-dose treatment regimen.
  Assumptions/data used:
  - 50% incidence of severe neutropenia in *28/*28 heterozygous patients (source: Iyer and Innocenti studies)

- 20% dose reduction decreases the risk by 30% (dose reduction source: Innocenti proposal based on differences in SN-38 exposure and similar dose reduction in practice in non-genotyped patients on development of severe neutropenia/toxicity; risk reduction source: estimate)
- Hospitalisation was required for 25% of the patients with severe neutropenia
- The adverse-event-related mortality rate among patients with febrile neutropenia was 7%
- No negative effect on survival after reduction of irinotecan dose (due to genotype or on development of severe neutropenia)
- Incremental cost effectiveness ratio (ICER) < US$ 20,000-1,000,000 per quality adjusted life year gained is cost-effective

- Dose dependence

  Two of the three meta-analyses that investigated grade 3-4 neutropenia showed that the risk of neutropenia was also elevated at low doses (Liu 2014 and Hu Clin Cancer Res 2010; Hoskins 2007). Two of the three meta-analyses that investigated grade 3-4 diarrhoea showed that the risk was elevated at high doses, but not at low doses (< 150 or 125 mg/m^2) (Liu 2014 and Hu Eur J Cancer 2010; Hoskins 2007). The meta-analysis of Hoskins 2007 also did not find an elevated diarrhoea risk at high doses. For *28, the meta-analysis of Yang 2018 found the risk of severe toxicity (including neutropenia and diarrhoea) to be elevated at high doses (> 150 mg/m^2), but not at low doses (< 150 mg/m^2). However, for *6 this meta-analysis found the risk to be increased at both high and low doses, with the ORs being higher at low doses. The most common doses used in the Netherlands are high doses (180 of 350 mg/m^2).

  Various studies use various dosing regimens and combination regimens which may influence the extent and severity of the adverse events diarrhoea and neutropenia. In general, patients on weekly irinotecan dosing regimens develop diarrhoea more frequently and those on three-weekly regimens develop neutropenia more frequently. [Fuchs et al. J Clin Oncol 2003;21:807-14, Vanhoefer et al. J Clin Oncol 2001;19:1501-18.] Three-weekly and two-weekly dosing regimens are most common in the Netherlands.

National Cancer Institute Common Toxicity Criteria (NCI-CTC)

	grade 1 = B	**grade 2 = C**	**grade 3 = D**	**grade 4 = E**	**grade 5 = F**
Diarrhoea	Increased stool frequency by < 4; slight increase in stoma output	Increased stool frequency by 4-6; moderate increase in stoma output; no effect on daily activities	Increased stool frequency by ≥ 7; incontinence; IV fluid ≥ 24 hours; hospitalisation; severe increase in stoma output; effect on daily activities	Life-threatening consequences (e.g. haemodynamic collapse)	Death
Neutropenia	> 1.5x10^9/L	< 1.5-1.0x10^9/L	< 1.0-0.5x10^9/L	< 0.5x10^9/L	Death
Leukopenia	> 3.0x10^9/L	< 3.0-2.0x10^9/L	< 2.0-1.0x10^9/L	< 1.0x10^9/L	Death
Thrombocytopenia	> 75x10^9/L	75-50x10^9/L	50-25x10^9/L	< 25x10^9/L	Death
Febrile neutropenia	-	-	Present	Life-threatening consequences (e.g. septic shock, hypotension, acidosis, necrosis)	Death

ULN = upper limit of normal

Date of literature search: 19 March 2021.

	Genotype	**Code**	**Gene- drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	*1/*28	4 F	Yes	No	7 June 2021
	*28/*28	4 F	Yes	Yes	
	IM	4 E	Yes	No	
	PM	4 E	Yes	Yes	

Mechanism:

Irinotecan is a prodrug that is converted predominantly by carboxylesterases to the active metabolite SN-38, which has 100-1000-fold higher activity than irinotecan itself. Irinotecan is also metabolised by CYP3A4/5 to inactive metabolites.

SN-38 is glucuronidated to the inactive metabolite SN-38-glucuronide by glucuronosyltransferases. SN-38 is predominantly metabolised by UGT1A1 and also by UGT1A6, UGT1A7, UGT1A9 and UGT1A10.

A UGT1A1 genetic polymorphism may change the plasma concentration of irinotecan, SN-38 and SN-38 glucuronide.

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 consider genotyping 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	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	++
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	++
• NNG ≤ 10	+++	
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+
Corresponding Clinical Implication Score:		Essential