Treatment optimisation and pharmacogenetics of systemic and intraperitoneal chemotherapy in colorectal cancer

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CHAPTER 3

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction between *UGT1A1* and irinotecan

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ABSTRACT

The Dutch Pharmacogenetics Working Group (DPWG) aims to facilitate PGx implementation by developing evidence-based pharmacogenetics guidelines to optimize pharmacotherapy. This guideline describes the starting dose optimization of the anti-cancer drug irinotecan to decrease the risk of severe toxicity, such as (febrile) neutropenia or diarrhoea. Uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1 encoded by the *UGT1A1* gene) enzyme deficiency increases risk of irinotecan-induced toxicity. Gene variants leading to UGT1A1 enzyme deficiency (e.g. *UGT1A1*6*, **28* and **37*) can be used to optimize an individual's starting dose thereby preventing carriers from toxicity. Homozygous or compound heterozygous carriers of these allele variants are defined as *UGT1A1* poor metabolisers (PM). DPWG recommends a 70% starting dose in PM patients and no dose reduction in IM patients who start treatment with irinotecan. Based on the DPWG clinical implication score, *UGT1A1* genotyping is considered "essential", indicating that *UGT1A1* testing must be performed prior to initiating irinotecan treatment.

INTRODUCTION

The role of heritable genetic variation on drug response is referred to as pharmacogenetics (PGx). Personalized medicine, also known as precision medicine, can be achieved with the use of PGx information. Knowledge of an individual's genetic composition for drug metabolizing enzymes, drug transporters, receptors or effector proteins may be used to guide pharmacological treatment. To implement the use of PGx in a clinical setting, guidelines informing physicians are essential. In order to accommodate, the Royal Dutch Pharmacists Association (KNMP) has appointed the Dutch Pharmacogenetics Working Group (DPWG) in 2005, a group of 15 professionals consisting of (clinical) pharmacists, physicians, a general practitioner, clinical pharmacologists, clinical chemists and epidemiologists [1]. The role of the DPWG is to develop evidence-based PGx-guided therapeutic recommendations based on systematic literature review and to implement these into computerized systems used nationwide in The Netherlands for medication prescription, dispensing and monitoring. In order to meet the public request for this information also outside the Dutch pharmacist and physician systems, the DPWG guidelines and future updates are published [2–5].

The current guideline presents the gene-drug interaction between *UGT1A1* and the anti-cancer drug irinotecan. The pharmacotherapeutic rationale for use of irinotecan as well as the cost-effectiveness of PGx-guided dosing is outside the scope of this guideline. This manuscript provides information on the development of this guideline and presents an overview of the PGx therapeutic recommendations. Background information of irinotecan and of the *UGT1A1* gene and its genetic variation is provided. This genetic information is followed by the evidence from literature on the gene-drug interaction between *UGT1A1* and irinotecan. Finally, therapeutic recommendations for the clinic and clinical decision support systems are provided. These DPWG PGx-guided recommendations are also compared to other international guidelines. The goal of this DPWG recommendation is to individualize the starting dose of irinotecan thereby decreasing the risk of severe and potentially fatal toxicity.

DRUG: IRINOTECAN

Irinotecan is a commonly applied anticancer drug and is registered for first-line treatment of pancreatic cancer, the second-line treatment of advanced and metastatic colorectal cancer and several other cancer types, including lung cancer and Ewing sarcoma. Of all treated patients, up to 40% experience common Toxicity Criteria grade ≥ III delayed diarrhoea, and up to 50% of the patients experience grade ≥ III neutropenia [6, 7].

Irinotecan is a prodrug that is converted predominantly by carboxylesterases (CES) in the liver and intestines to the active metabolite SN-38, which has 100 to 1,000-fold higher activity compared to irinotecan. Irinotecan is, besides by CES, also metabolised by CYP3A4/5 in the liver to inactive metabolites. SN-38 is predominantly glucoronidated by UGT1A1 and also by UGT1A6, UGT1A7, UGT1A9 and UGT1A10 to the inactive metabolite SN-38-glucuronide. A schematic overview of the metabolism of irinotecan and its active metabolite SN-38 is depicted in **Figure 3.1**.

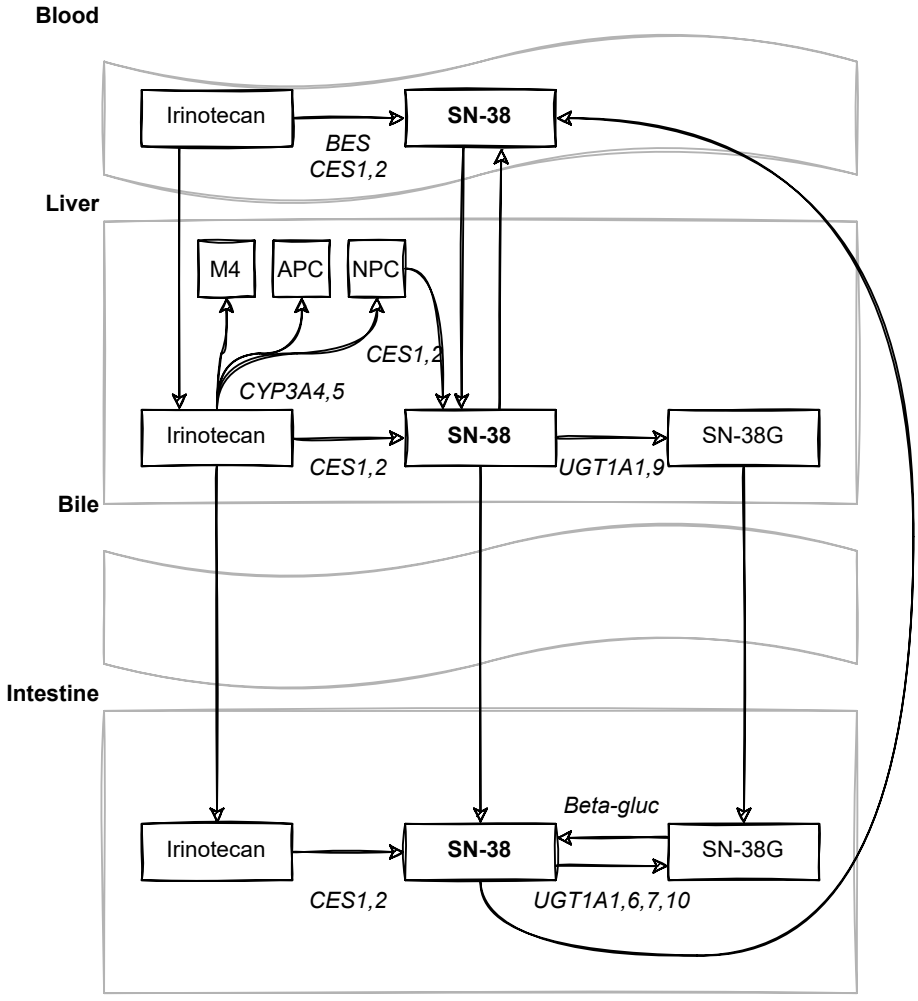

Figure 3.1: Irinotecan metabolism. Irinotecan and its metabolites are presented in rectangles. The active metabolite, SN-38, is presented in bold letters.

Abbreviations: APC = 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin, BES = butyrylcholinesterase, CES = carboxylesterase, CYP = cytochrome P450 enzymes, NPC = 7-ethyl-10-[4-(1-piperidino)-1-amino] carbonyloxycamptothecin, UGT = uridine diphosphate glucuronosyltransferase, SN-38G = SN-38 glucuronide, beta-gluc = beta-glucuronidase.

GENE: URIDINE DIPHOSPHATE GLUCURONOSYL TRANSFERASE 1A1 (*UGT1A1*)

The *UGT1A1* gene coding for the UGT1A1 enzyme is located on chromosome 2 (2q37.1) and consists of 5 exons, of which the first exon at the 5' terminus is unique and exons 2 to 5 are shared with the genes *UGT1A6* and *UGT1A9*.

Many variants exist for *UGT1A1*; more than 100 different alleles have been identified/described in the literature and are often associated with Gilbert syndrome or Crigler-Najjar syndrome. A number of these alleles and their functionality are listed in **Supplementary Table S3.1**. The most studied variation in *UGT1A1* involves a repeat in the promoter region of the *UGT1A1* gene. The number of "TA" tandem repeats in the TATA box of the promoter region varies. The UGT1A1 activity decreases with an increasing number of TA repeats. For example, the *28 variant contains 7 TA repeats instead of 6 TA repeats before the last TA in the TATA box and results in a 67 to 82 percent lower gene expression [8, 9].

The frequency of the various *UGT1A1* alleles shows considerable inter-ethnic variability. The variant allele *28 is abundant in inhabitants in South Asia (41%) and much less frequently in the rest of Asia (10–12%) [10]. The prevalence in Europeans ranges from 22 to 39% [10]. The variant allele *6 is common in several Asian populations and also strongly associated with reduced enzyme activity [11–13]. *UGT1A1*6* has allele frequencies in Japanese, Korean and Chinese populations of 13, 23 and 23%, respectively [14]. An overview of *UGT1A1* allele and genotype frequencies in different populations based on these references and the gnomAD database, is provided in **Supplementary Table S3.2**.

TRANSLATION OF GENOTYPE TO PREDICTED PHENOTYPE

The DPWG has concluded that variants resulting in decreased UGT1A1 metabolic capacity have sufficient evidence to be implemented into clinical care. In the case of the *36 variant, an allele that results in increased UGT1A1 metabolic capacity, there are currently no data to suggest that this results in clinically relevant effects. Therefore, for the time being, this is considered an allele with normal function. Notwithstanding, higher doses of irinotecan could potentially be indicated, but this requires further research. For *UGT1A1*, three different phenotypes are distinguished: normal metaboliser (NM), intermediate metaboliser (IM) and poor metaboliser (PM). The two phenotypes with reduced metabolic capacity (IM and PM) are further subdivided based on whether or not *28 is the only gene variant that results in

decreased metabolic capacity. The genotype-phenotype translation is presented in **Table 3.1**. In addition, an extensive genotype-phenotype translation table that can be used to programme the translation of genotype results into predicted phenotypes in laboratory information systems is provided in **Supplementary Table S3.3**.

Table 3.1: Genotype-phenotype translation

Genotype		Phenotype predicted based on genotype
Description	Examples	
Two alleles with normal (or increased) enzyme activity	*1/*1, *1/*36	NM
*28 and one allele with normal (or increased) enzyme activity	*1/*28, *28/*36	IM (*1/*28)
One allele with decreased enzyme activity other than *28 and one allele with normal (or increased) enzyme activity	*1/*6, *1/*37, *36/*37	IM other
Two *28 alleles	*28/*28	PM (*28/*28)
Two alleles with decreased enzyme activity, of which at least one is not *28	*6/*6, *6/*28, *28/*37	PM other

NM = Normal metaboliser, IM = intermediate metaboliser, PM = poor metaboliser.

GENE-DRUG INTERACTION

Pharmacological mechanism

UGT1A1 is mainly present in the liver and intestines and is the most important enzyme to inactivate irinotecan's active metabolite SN-38. Decreased UGT1A1 activity leads to increased concentrations of SN-38, which in turn could lead to an increased risk of severe toxicities, such as (febrile) neutropenia and diarrhoea [15]. Variations in the *UGT1A1* gene can result in reduced, or even absent enzyme activity. For example, the *UGT1A1*28/*28* genotype leads to an 18–159% increased systemic exposure of SN-38, and SN-38 metabolic clearance decreases by 61% [16–21].

SUPPORTING BODY OF EVIDENCE

A detailed description of the methods used for literature collection, assessment and preparation of the gene-drug monograph has previously been published [1]. In brief, a systematic review of literature was performed, relevant articles were summarized, and therapeutic recom-

mendations were proposed by a scientist of the Royal Dutch Association for the Advancement of Pharmacy (MN). The performed search strategy can be found in **Supplementary Material S3.1** and was conducted until March 19, 2021. The quality of evidence was scored on a 5-point scale ranging from 0 (lowest) to 4 (highest) and the impact of the clinical effect was scored on a 7-point scale ranging from AA# (positive effect) to F (highest negative effect). This clinical impact scale (AA#-F) runs parallel to the Common Terminology Criteria for Adverse Events (CTCAE); where CTCAE grade 5 severity is equal to clinical relevance score F (death) and CTCAE grade 1 severity is equal to clinical relevance score B. The clinical relevance score additionally includes the scores AA#, AA and A, since these do not exist in the CTCAE. These regard AA#: "Positive clinical effect", AA: "No significant clinical and/or kinetic effect", and A: "Significant kinetic effect or not clinically relevant negative effect". The summaries and scores of the articles reviewed to devise this guideline are described in **Supplementary Table S3.4**. The summary and scores of each article were checked by two independent DPWG members. The DPWG made the final decision on the therapeutic recommendations. DPWG guidelines are checked for agreement with current evidence every 5 years in general. An updated version of the guideline will be published if recommendations are altered.

The initial literature search was performed on September 18, 2006, followed by searches on October 27, 2008, March 19, 2014, July 20, 2017 and March 19, 2021. Given the large number of articles, the only articles included after July 2006 were those that included at least 25 subjects with one or more *28 alleles. The only clinical studies included for the period 2008–2017 were meta-analyses, as large individual studies (n>200) were already included in the meta-analyses. From 2008 to 2014 only meta-analyses with mainly White 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. For the period after 2014, meta-analyses were included if the effect of *28 was analysed, either alone or in combination with *6. 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. Pharmacokinetic 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 Whites) (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.

GENERAL CONCLUSION OF EVIDENCE

For *28/*28 and "PM other", there is strong evidence that these genotypes are associated with an increased risk of grade ≥3 toxicity such as neutropenia or diarrhoea. All nine meta-analyses investigating adverse events and 16 of the 23 included studies reported this increased risk. In addition, all seven meta-analyses and three studies investigating the effect of *28/*28 and/or *6/*6 and/or *6/*28 compared with all other genotypes, found that this toxicity risk was also increased for *28/*28 and/or PM patients compared to all other patients. With regard to efficacy, 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 treatment. See **Supplementary Table S3.4** and **S3.5** for a detailed description of the literature and the rationale of the therapeutic recommendations. In addition, recently the results of a prospective implementation study of *UGT1A1* genotype-guided dosing of irinotecan in PM patients were published showing that *UGT1A1* genotype-guided dosing of irinotecan in PM patients with applying a 30% dose reduction significantly improved safety while maintaining therapeutic drug exposure [22].

In summary, for *28/*28 and "PM other" there is ample evidence for an increased risk of serious adverse events such as neutropenia or diarrhoea at normal doses (also when compared to all other genotypes/phenotypes), while convincing evidence for an increased efficacy has not been demonstrated. Therefore, the DPWG concludes that a *UGT1A1* gene-drug interaction is present and that it necessitates a dose adjustment of irinotecan. Ongoing debate persists on whether or not there is a clinically relevant higher risk of toxicity in PM patients treated with lower dosages of irinotecan (<150 mg/m^2). However, two meta-analyses [23,24] indicate that the risk of grade 3–4 neutropenia is also elevated at lower doses of irinotecan and therefore the DPWG recommend dose adjustment of irinotecan in all dosing categories.

For *1/*28 and "IM other", a similar amount of evidence is present as for *28/*28 and "PM other". See **Supplementary Table S3.4** and **S3.5** for a detailed description of the literature and the rationale of the therapeutic recommendations. However, *1/*28 is the major group among White populations. The initial standard irinotecan dose derived in earlier phase I studies was therefore mainly driven by the *1/*28 genotype. This is confirmed by Lu et al. 2015 [25], showing that most *1/*28+*1/*1 patients tolerate the standard dose, whereas *28/*28 patients did not. Furthermore, there were negligible dose adjustments calculated for *1/*28 compared to all genotypes (a weighted mean calculated dose adjustment to 95% of the dose for all patients based on 6 studies with a total of 112 patients with the *1/*28

genotype) (**Supplementary Table S3.5**). This means that a priori dose reduction for patients with *1/*28 would lead to subtherapeutic doses for this patient group. Because the kinetic and clinical effects of *28 and *6 are comparable, the same holds true for IM predicted phenotype as a whole. Therefore, the DPWG concludes that a gene-drug interaction is present, but that therapy adjustment is neither required nor advisable in *UGT1A1* IM patients.

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, an increase for *1/*1 patients has not yet proven to be useful. Therefore, the DPWG decided to refrain from a recommendation for *1/*1.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

The DPWG therapeutic recommendations to optimize the starting dose of irinotecan in patients known to have a variant UGT1A1 predicted phenotype is summarized in **Table 3.2**. In brief, UGT1A1 PM patients, including *28/*28, should receive a 70% starting dose of irinotecan, with the number of 70% primarily based on kinetic data and early dose-finding studies as described below. Further dose titration is possibly guided on neutrophil count and clinical tolerance. For *UGT1A1*1/*28* and *UGT1A1* "IM other" patients no dose reduction is recommended.

Table 3.2: Summary therapeutic recommendations based on *UGT1A1* predicted phenotype for irinotecan

UGT1A1 predicted phenotype	Therapeutic recommendation
PM (*28/*28)	Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
PM other	Start with 70% of the normal dose[a]. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
IM (*1/*28)	No action required
IM other	No action required

IM = intermediate metaboliser, PM = poor metaboliser.
[a] The normal dose is defined as the dose the patient would receive if he/she would not have a gene variant.

The dose calculation for *28/*28 was based on the SN-38 exposure (area under the curve (AUC)) or clearance in 6 studies with a total of 28 patients with *28/*28. The weighted mean of the calculated dose adjustment is a dose of 58% (range 39–85%, median 53%) of the dose for *1/*1 and a dose of 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 to prevent subtherapeutic doses, the calculated dose compared to all patients was chosen. This is translated into a starting dose of 70% which is more achievable in clinical practice (**Supplementary Table S3.5**). The SN-38 glucuronide/SN-38 area under the curve (AUC) ratios are comparable for *28/*28 and *6/*6, suggestive of a similar effect size on irinotecan metabolism [26]. Therefore, the recommendations for the "PM other" predicted phenotype (for example caused by *6), is the same as the recommendations for the *28/*28 genotype, respectively.

More information on the rationale, kinetic and clinical consequences of these therapeutic recommendations are depicted in **Supplementary Table S3.5**.

Supplementary Table S3.6 provides an overview of suggested pop-up (or look-up) texts for electronic prescribing systems for pharmacists and physicians. These can be used to program alerts into the clinical decision support system (CDSS).

IMPLICATIONS FOR CLINICAL PRACTICE

Ongoing debate persists whether and which single gene-drug pairs should be implemented into routine care. Points of debate include the amount of evidence that is necessary supporting effectiveness of genotyping prior to initiating therapy, cost-effectiveness of PGx testing in the pre-therapeutic setting and its reimbursement [27]. As a consequence, gene–drug pairs which are ready for implementation are hampered in application in clinical practice [28]. In an effort to overcome this inconclusiveness and to direct clinicians on whether or not to order relevant PGx genotyping tests before initiating therapy, the DPWG has developed the Clinical Implication Score. The DPWG Clinical Implication Score for a gene–drug pair can be scored as: essential, beneficial or potentially beneficial. These categories are clarified in **Supplementary Table S3.7**. The development of these categories and the systematic scoring criteria are discussed elsewhere [29]. In brief, the implications for clinical practice are based on four criteria: the clinical effect associated with gene–drug interaction; the level of evidence supporting the associated clinical effect; the number needed to genotype (NNG) in the Dutch population; and the availability of and type of PGx information in the drug label

issued by the Dutch drug agency CBG-MEB. The scores provided for each of these criteria by the DPWG can be found in **Supplementary Table S3.7**. Only gene-drug interactions which are actionable are subject to receiving a Clinical Implication Score.

The Clinical Implication Score of the gene-drug interaction between UGT1A1 and irinotecan is 8 out of the maximum of 10 points. This indicates that genotyping before starting irinotecan is considered "**essential**" for drug safety. Genotyping must be performed before drug therapy has been initiated to guide dose selection. The feasibility and clinical benefit of such an approach has also recently been demonstrated. A recent prospective implementation study on *UGT1A1* genotype-guided dosing of irinotecan in PM patients showed that genotype-guided dosing in PM patients increases safety, provides therapeutic drug exposure, and is cost-effective, and supports the recommendation of a 70% starting dose in UGT1A1 PM patients [22].

DIFFERENCES BETWEEN AVAILABLE PHARMACOGENETIC GUIDELINES

To the best of our knowledge there are two other pharmacogenetic guidelines available on the gene-drug interaction of irinotecan and *UGT1A1*. First, a guideline by the French joint working group comprising the National Pharmacogenetics Network (RNPGx) and the Group of Clinical Onco-pharmacology (GPCO-Unicancer) [30]. Second, an Italian guideline by the Italian association of medical oncologists (AIOM) and the Italian Society of Pharmacology (SIF) [31]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has no guideline available, but indicates this gene-drug interaction as an actionable PGx [32]. Both guidelines are shortly discussed below.

RNPGx and GPCO-Unicancer

The genotype-phenotype translation in the RNPGx/GPCO guideline is in line with the DPWG guideline; the *36 allele can be interpreted as a *1 allele and the *37 allele as a *28 allele. In addition, in both guidelines pre-treatment *UGT1A1* genotyping is strongly recommended and the advised dose reduction at the first cycle for *28/*28 patients is similar, namely 25–30%.

However, the RNPGx/GPCO guideline does not recommend pre-therapeutic *UGT1A1* genotyping for low irinotecan doses (<180 mg/m^2) because haematological and gastrointestinal toxicities are quite similar regardless of the genotype for low irinotecan doses. In contrast, the DPWG concluded that the risk of grade 3–4 neutropenia is also elevated at lower doses of irinotecan based on two meta-analyses [23, 24] and therefore recommends to genotype all

patients treated with irinotecan. Moreover, in the RNPGx/GPCO guideline it is recommended that *28/*28 patients must not receive high-dose irinotecan (≥240 mg/m^2) because of a much higher risk of haematological toxicity (neutropenia) compared to other genotypes, whereas the DWPG guideline does not advocate a contra-indication for high-dose irinotecan in these patients.

AIOM and SIF

This Italian guideline only provides guidance on the *28 gene variant of *UGT1A1*. They recommend a dose reduction of 30% in *28/*28 patients which is in line with the current DPWG guideline.

CONCLUSION

In conclusion, the DPWG recommends a 70% starting dose in PM patients that start treatment with irinotecan. In IM patients, an a priori dose reduction is not recommended. Based on the DPWG clinical implication score, *UGT1A1* genotyping is considered "essential", therefore directing towards pre-therapeutic *UGT1A1* testing in patients intended for treatment with irinotecan.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Search terms used to perform the literature review of the *UGT1A1* – irinotecan interaction

Search strategy

PubMed was searched for English, Dutch and German articles. For PubMed-searches with the following term: '("humans"[Mesh Terms])' the database was also searched without this term in order to find recent articles.

Complete search strings

Search performed in 2006: irinotecan AND UGT1A1

Search performed in 2008 and 2014: ("irinotecan"[Substance Name] OR irinotecan[Text Word]) AND (UGT* OR "bilirubin uridine-diphosphoglucuronosyl transferase 1A1"[Substance Name] OR "Glucuronosyltransferase"[MeSH] OR "bilirubin"[MeSH Terms] OR bilirubin[Text Word] OR metabolizer OR metaboliser OR polymorph* OR "Polymorphism, Genetic"[MeSH] OR "Pharmacogenetics"[MeSH]) AND (English[lang] OR German[lang] OR Dutch[lang]) AND ("humans"[Mesh Terms])

Search performed in 2017: ("irinotecan" [Supplementary Concept] OR irinotecan) AND ("UGT1A1 enzyme" [Supplementary Concept] OR UGT1A1 OR 1A1) AND (English[lang] OR German[lang] OR Dutch[lang])

Search performed in 2021: ("Irinotecan"[Mesh] OR irinotecan) AND ("UGT1A1 enzyme" [Supplementary Concept] OR UGT1A1 OR 1A1) AND (English[lang] OR German[lang] OR Dutch[lang])

Supplementary Table S3.1: *UGT1A1* alleles and metabolic capacity [1]

Metabolic capacity	*allele	rs-number	HGVS reference sequence		
			NM_000463.3	NP_000454.1	NC_000002.12
Increased functionality	*36	rs3064744	Not applicable	Not applicable	g.233760235TA[6]
Fully functional	*1 (= wild-type)	Not applicable	Not applicable	Not applicable	g.233760235TA[7]
Reduced functionality	*6	rs4148323	c.211G>A	p.Gly71Arg	g.233760498G>A
	*7	rs34993780	c.1456T>G	p.Tyr486Asp	g.233772413T>G
	*8	rs72551343	c.625C>T	p.Arg209Trp	g.233760912C>T
	*9	rs72551348	c.992A>G	p.Gln331Arg	g.233767161A>G
	*12	rs72551341	c.524T>A	p.Leu175Gln	g.233760811T>A
	*27	rs35350960	c.686C>A	p.Pro229Gln	g.233760973C>A
	*28	rs3064744	Not applicable	Not applicable	g.233760235TA[8]
	*29	rs55750087	c.1099C>G	p.Arg367Gly	g.233768234C>G
	*30	rs111033541	c.44T>G	p.Leu15Arg	g.233760331T>G
	*32	rs139607673	c.1006C>T	p.Arg336Trp	g.233767858C>T
	*33	rs72551347	c.881T>C	p.Ile294Thr	g.233767050T>C
	*34	rs1699317728	c.928A>G	p.Met310Val	g.233767097A>G
	*37	rs3064744	Not applicable	Not applicable	g.233760235TA[9]

Supplementary Table S3.1: ***Continued***

Metabolic capacity	*allele	rs-number	HGVS reference sequence		
			NM_000463.3	NP_000454.1	NC_000002.12
Fully dysfunctional (null alleles)	*2	rs587776761	c.877_890delinsA	p.Tyr293fs	g.233767046_233767060delinsA
	*3	rs72551353	c.1124C>T	p.Ser375Phe	g.233768259C>T
	*4	rs72551350	c.1069C>T	p.Gln357Ter	g.233767921C>T
	*5	rs111033539	c.991C>T	p.Gln331Ter	g.233767160C>T
	*10	rs72551349	c.1021C>T	p.Arg341Ter	g.233767873C>T
	*11	rs62625011	c.923G>A	p.Gly308Glu	g.233767092G>A
	*13	rs587776762	c.510CTT[1]	p.Phe171del	g.233760797CTT[1]
	*14	rs72551345	c.826G>C	p.Gly276Arg	g.233761113G>C
	*15	rs7255342	c.529T>C	p.Cys177Arg	g.233760816T>C
	*16	rs72551351	c.1070A>G	p.Gln357Arg	g.233767922A>G
	*17	rs72551354	c.1143C>G	p.Ser381Arg	g.233768278C>G
	*18	rs72551355	c.1201G>C	p.Ala401Pro	g.233768336G>C
	*19	rs1699508733	c.1005G>A	p.Trp335Ter	g.233767857G>A
	*20	rs72551352	c.1102G>A	p.Ala368Thr	g.233768237G>A
	*22	rs758873309	c.875C>T	p.Ala292Val	g.233767044C>T
	*25	rs281865418	c.840C>A	p.Cys280Ter	g.233761127C>A
	*31	rs1559415403	c.1160_1161delinsGT	p.Pro387Arg	g.233768295_233768296delinsGT

[1] https://www.pharmacogenomics.pha.ulaval.ca/wp-content/uploads/2015/04/UGT1A1-allele-nomenclature.html, accessed at January, 2022.

Supplementary Table S3.2: *UGT1A1* allele and genotype frequencies

Population group/region	Prevalence of genotype (%)								Allele frequency (%)		
	*1/*1 TA6/ TA6	*1/*28 TA6/ TA7	*28/*28 TA7/ TA7	*36/*1 TA5/ TA6	*36/*28 TA5/ TA7	*36/*37 TA5/ TA8	*1/*37 TA6/ TA8	*28/*37 TA7/ TA8	*28	*6	*37
Whites	34–38	46–55	11–13	0–2	0	0	0	0–2	33–36		0-2.8
The Netherlands (Whites)	37	54	9						36		
Europe	30–50	40–60	5–15						22–39		
Europe (without Finland)									32	0.2	0.07
Finland									42	4.6	0.05
Africa	20–60	30–50	6–18	4–12	7–8	1–2	3–8	1–14	24–42		1.2–29
African-American	26	33–37	13–19	0–2	5	3	4–15	5–6	36–44		5.7–8.3
African/ African-American									40	0.07	5
Asia	25–75	15–60	2–20	0	0	0	0	0	14–45		0
East Asia									12	15.3	
Japan									10.4	22.2	
South Asia									41	2.0	0.2
South America	55	30	12						27		
Latin-American/ American, mixed ethnicity									31	2.4	0.4
Pacific	75–95	5–20	2						4.5–12		
Ashkenazi Jewish									38	0.5	

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Supplementary Table S3.3: Genotype to predicted phenotype translation to be programmed into laboratory information system

Genotype	rs number variants	Nucleotide at position	Predicted phenotype
UGT1A1: WILDTYPE/WILDTYPE	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C G:G -:-	*1/*1 (TA6/TA6)
UGT1A1:*28/*37/*28/*37	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C G:G TA:TA	*28/*28 (TA7/TA7)
UGT1A1:WILDTYPE/*28/*37	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C G:G -:TA	*1/*28 (TA6/TA7)
UGT1A1:*27/*27	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	A:A G:G -:-	PM otherwise
UGT1A1:WILDTYPE/*27	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:A G:G -:-	IM otherwise
UGT1A1:WILDTYPE/*27_WILDTYPE/*28/*37	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:A G:G -:TA	PM otherwise
UGT1A1:*6/*6	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C A:A -:-	PM otherwise
UGT1A1:WILDTYPE/*6	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C G:A -:-	IM otherwise
UGT1A1:WILDTYPE/*6_WILDTYPE/*28/*37	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:C G:A -:TA	PM otherwise
UGT1A1:WILDTYPE/*27_WILDTYPE/*6	*UGT1A1*_rs35350960 *UGT1A1*_rs4148323 *UGT1A1*_rs8175347	C:A G:A -:-	PM otherwise

This table includes *UGT1A1* alleles with a minor allele frequency ≥1% in either the White, African or Asian population.

According to the allele definition table of PharmGKB, there is no allele including two of the polymorphisms (https://www.pharmgkb.org/haplotype/PA166115865, accessed on 16 December 2022). This suggests that alleles including two or more of these polymorphisms are either very rare or non-existent. For this reason, genotypes with 3 or 4 polymorphisms were not included in the translation table. In addition, in compound heterozygotes, both polymorphisms were considered to be on different alleles.

Supplementary Table S3.4: Literature review of *UGT1A1*-irinotecan interactions supporting the therapeutic guideline to reduce the starting dose in PM patients

The table below follows the KNMP nomenclature for UGT1A1 gene variants. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the original publications.

Reference	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. PMID: 29932297.	Level of evidence score: 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 *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 homo-zygotes compared to no variant allele)) they investigated possible publication bias. No publication bias analyses were performed for the subgroups.	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.'

*28/*28: CTC-AE 4
*1/*28: CTC-AE 4

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 (2.25–5.39) (S)	OR=1.81 (1.46–2.25) (S)	
	<150 mg/m^2	NS	NS	
Severe toxicity	All tumour types	OR=2.76 (1.86–4.09) (S)	OR=1.68 (1.37–2.06) (S)	
	Digestive system	OR=2.90 (1.95–4.30) (S)	OR=1.73 (1.40–2.15) (S)	
	Respiratory system	NS	NS	

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.

There was no publication bias according to the Egger's test.

PM: CTC-AE 4
IM: CTC-AE 4

ORs (95% CI) for *1/*6 and *6/*6 versus *1/*1:

		*6/*6	*1/*6	Incidence for *1/*1 (% of patients)
Neutropenia grade III–IV		OR=3.03 (2.05–4.47) (S)	OR=1.95 (1.34–2.85) (S)	17%
Diarrhoea grade III–IV		OR=4.03 (1.98–8.32) (S)	OR=1.98 (1.26–3.11) (S)	8.6%
Severe toxicity	Asians (= the only ethnicity in the studies)	OR=3.16 (2.25–4.44) (S)	OR=1.95 (1.42–2.66) (S)	
Severe toxicity	All irinotecan doses	OR=3.17 (2.24–4.48) (S)	OR=2.08 (1.46–2.97) (S)	

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

			>150 mg/m^2	OR=2.91 (2.02–4.18) (S)	OR=1.82 (1.28–2.57) (S)	
			<150 mg/m^2	OR=9.42 (2.43–36.5) (S)	OR=3.49 (1.28–9.58) (S)	
		Severe toxicity	All tumour types	OR=3.21 (2.20–4.67) (S)	OR=1.75 (1.22–2.52) (S)	
			Digestive system	OR=3.00 (2.04–4.42) (S)	OR=1.66 (1.18–2.35) (S)	
			Respiratory system (only 1 study)	OR=18.2 (1.56–212) (S)	OR=12.0 (1.02–141) (S)	
		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.				
		There was no publication bias according to the Egger's test.				
ref. 2 Tejpar S et al. Clinical and pharmacogenetic determinants of 5-fluorouracyl/ leucovorin/irinotecan toxicity: results of the PETACC-3 trial. Eur J Cancer 2018;99:66-77. PMID: 29909091.	Level of evidence score: 4	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 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:				Authors' conclusion: 'We found that a complex of risk 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.'

	*28/*28: CTC-AE 4	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):		
				incidence for *1/*1+ *1/*28
		Neutropenia grade III–IV	OR_{adj}=2.89 (1.65–5.07) (S)	28% of patients
			Kaplan-Meier curve analysis showed *28/*28 to be associated with more frequent and earlier neutropenia grade III–IV (S).	
			In univariate analysis, there was no difference between *1/*1 and *1/*28.	
			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%).	
		Neutropenia grade IV	OR_{adj}=2.33 (1.03–5.24) (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 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-	

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

	*1/*28: CTC-AE 4		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 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.			
ref. 3 Chen X et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment out-come in Asians with lung cancer: a meta-analysis. Cancer Chemother Pharmacol 2017;79:1109-1117. PubMed PMID: 28502040.	Level of evidence score: 3	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/m2. 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 White), 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		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

<table>
<tr>
<td></td>
<td>*28/*28: CTC-AE 4
*1/*28: Clinical Relevance Score AA</td>
<td>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:
<table>
<tr><td colspan="4">ORs (95% CI) for *1/*28 and *28/*28 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>Diarrhoea</td><td>OR=5.93 (1.46–24.0) (S)</td><td>NS</td><td>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><td></td></tr>
<tr><td>Neutropenia</td><td>NS</td><td>NS</td><td>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><td></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>
</td>
<td>TR.’</td>
</tr>
</table>

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

<table>
<tr><td></td><td>PM: CTC-AE 4
IM: CTC-AE 4</td><td>ORs (95% CI) for *1/*6 and *6/*6 versus *1/*1:<table>
<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>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><td></td></tr>
<tr><td>Neutropenia</td><td>NS</td><td>NS</td><td>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><td></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>Level of evidence score: 4</td><td colspan="2">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 White 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, 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.</td><td>Authors’ conclusion: ‘Our data showed that the UGT1A1*28 polymorphism had a significant relation-ship with toxicity and response to irinotecan-based chemotherapy. This polymorphism may be useful as a monitoring index for cancer patients receiving irinotecan-based chemotherapy.’</td></tr>
</table>

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:

ORs (95% CI) versus *1/*1:			
	*28/*28	*1/*28	incidence for *1/*1 (% of patients)
Diarrhoea			
All patients	OR=3.97 (1.88–8.38) (S)	OR=1.56 (1.25–1.96) (S)	9.3%
	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).		
White patients	NS	NS	13%
	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).		
Asian patients	OR=8.98 (5.21–15.5) (S)	OR=1.85 (1.37–2.50) (S)	8.2%
	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	OR=3.53 (1.54–8.09) (S)	OR=1.60 (1.11–2.31) (S)	

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

	*28/*28: CTC-AE 4 *1/*28: CTC-AE 4	patients	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				
		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).			
		White 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).			
	*1/*28 + *28/*28: Clinical Relevance Score AA[#]	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				
		All patients	OR=1.20 (1.07–1.34) (S) for *1/*28+*28/*28 versus *1/*1			
		White 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 - White 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 - White 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			

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

		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, neutropenia and tumour response was respectively 763, 1162 and 1078 patients. The number of patients in these meta-analyses were higher.	
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.	Level of evidence score: 3	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 irinotecan) 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% decrease 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	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 favourable clinical outcome without significant AEs.'

<table>
<tr>
<td></td>
<td>*28/*28: Clinical Relevance Score A</td>
<td>(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:
<table>
<tr><td colspan="4">Results for *28/*28 on reduced initial dose compared to *1/*1+*1/*28 on normal initial dose:</td></tr>
<tr><td colspan="2"></td><td>*28/*28</td><td>value for *1/*1+ *1/*28 (incidence in % of patients or maximum dose)</td></tr>
<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</td>
<td>Level of evidence score: 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. FOLFI-RI (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</td>
<td>Authors' conclusion:
'In conclusion, the study demonstrates that UGT1A1*28 is unlikely to be strongly prognostic of overall survival for individuals</td>
</tr>
</table>

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: *Continued*

<table>
<tr>
<td>collaborative meta-analysis. Pharmacogenomics J 2014;14:424-31. PubMed PMID: 24709690.</td>
<td></td>
<td>(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 progression, 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>
</table>
</td>
<td>treated with irinotecan. This is in contrast to the strong association previously reported between UGT1A1 *28 and irinotecan-related toxicity.’</td>
</tr>
</table>

	*28/*28: Clinical Relevance Score AA *1/*28: Clinical Relevance Score AA	Overall survival	NS	NS	
			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).		
		Progression-free survival	NS	NS	
			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).		
		One of more cycles with reduced irinotecan dose	NS	Trend for an increased risk (p=0.07) (NS)	
		For overall survival, there was no statistically significant 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 sub-groups 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			

Supplementary Table S3.4 continues on next page.

Supplementary Table S3.4: ***Continued***

		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.	Level of evidence score: 3 *28/*28 + PM: CTC-AE 4 PM: CTC-AE 4	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: *28/*28 + *6/*28 + *6/*6: OR=3.28 (95% CI: 2.15–4.98) (S) *6/*6: OR=3.28 (95% CI: 1.89–5.69) (S) 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) 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.	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.'
ref. 8	Level of evidence	Meta-analysis of 18 clinical trials with in total 1303 Asian patients treated with irinotecan. Irinotecan	Authors' conclusion:

<table>
<tr>
<td>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>score 3

*28 + *6: CTC-AE 4</td>
<td>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 ORG was calculated. ORG was defined such that ORG >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) after reducing heterogeneity to non-significant by removal of one of the studies (Onoue 2009) from the meta-analysis.</td></tr>
<tr><td colspan="4">For *28 + *6 and for *28, the heterogeneity between the studies was not significant.</td></tr>
</table>
</td>
<td>‘In Asians, a combination test of UGT1A1*6 and UGT1A1*28 might be a potential bio-marker of irinotecan-induced neutropenia, an observation that will need additional trials for confirmation.’</td>
</tr>
</table>

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Supplementary Table S3.4: ***Continued***

		For *6, the heterogeneity between the studies was mode-rate and statistically significant. There were no indications for publication bias. 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.	
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.	Level of evidence score: 3 *1/*28: CTC-AE 4 *28/*28: CTC-AE 4	A meta-analysis of 16 studies including a total of 2,328 mainly White 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 fluo-rouracil 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	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.'

		150 mg/m^2 (OR=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 White 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.	Level of evidence score: 3 *1/*28: Clinical Relevance Score AA *28/*28: Clinical Relevance Score 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.	Level of evidence score: 3	A meta-analysis of 12 studies including a total of 1,896 mainly White patients with colorectal cancer. Of the 12 studies included in the meta-analysis, 3 were also included separately in this risk analysis (Carlini,	Authors' conclusion: 'UGT1A1*28 polymorphism cannot

Supplementary Table S3.4 continues on next page.

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Association be-tween 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.	*1/*28: Clinical Relevance Score AA *28/*28: Clinical Relevance Score AA	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 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 White population. N.B.2: The most common irinotecan doses used in the Netherlands exceed 150 mg/m^2.	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 chemotherapy requires further validation.'
ref. 12 Dias MM et al. Impact of the UGT1A1*28 allele on response to irinotecan:	Level of evidence score: 4	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.	Authors' conclusion: 'An individual's response to irinotecan is unlikely to be

a systematic review and meta-analysis. Pharmacogenomics 2012;13:889-99. PubMed PMID: 22676194.	*1/*28: Clinical Relevance Score AA *28/*28: Clinical Relevance Score AA	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). 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.	affected by UGT1A1 *28 status.'
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.	Level of evidence score: 4 *1/*28: CTC-AE 4	A meta-analysis of 15 studies including a total of 1,998 mainly White 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	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.'

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Supplementary Table S3.4: ***Continued***

		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: CTC-AE 4	*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 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 White 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 be-tween UGT1A1-*28 polymorphism and	Level of evidence score: 3	A meta-analysis of 20 studies including a total of 1,760 patients (1,263 mainly White, 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	Authors' conclusion: 'Patients carrying UGT1A1*28 allele(s) are at an increased risk of irinotecan-induced severe diarrhoea. This

irinotecan-induced diarrhoea: a meta-analysis. Eur J Cancer 2010;46:1856-65. PubMed PMID: 20335017.		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 Whites, 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).	increased risk is only apparent in those who are administrated with medium or high irinotecan doses.'
	*1/*28: CTC-AE 4	*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 White 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 Whites 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 and all doses and for all patients and doses ≥125 mg/m^2.	
	*28/*28: CTC-AE 4	*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 Whites, there were no ethnicity subgroups.	

Supplementary Table S3.4 continues on next page.

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	PM: CTC-AE 4	*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 Whites, there were no ethnicity subgroups. *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, White 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 Whites 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. NOTE1: *28 is the most common allele variant in the White 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.	Level of evidence score: 4	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	Authors' conclusion: 'UGT1A1 polymorphisms were associated with variability in irinotecan pharmacokinetics.'

Cancer Chemother Pharmacol 2009;65:97-105. PubMed PMID: 19415281.	*1/*28: Clinical Relevance Score A *28/*28: Clinical Relevance Score A	*1/*28 versus *1/*1: - Dose-corrected SN-38 AUC0-48h 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 AUC0-48h increased by 109% (S; from 1.65 to 3.45 ng.hour/mL per mg/m^2)	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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: CTC-AE 4	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% and 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 mono-therapy or combination therapy. (The dose was mainly reduced in cycles 2 and 3 and 89% was due to gastro-intestinal 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	Level of evidence score: 3 (*28/*28 + *1/*28): CTC-AE 4	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 IFLa, 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

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metastatic colorectal carcinoma. Cancer 2008;112:1932-40.		- 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 into-lerable 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.	toxicities without affecting treatment outcome for patients with metastatic colorectal 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.	Level of evidence score: 3 (*28/*28 + *1/*28): Clinical Relevance Score 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	Level of evidence score: 3	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.	Authors' conclusion: 'The risk of experiencing irinotecan-induced hematologic toxicity for patients with a UGT1A1 *28/*28 genotype thus appears

2007;99:1290-5.	*28/*28: CTC-AE 4 *28/*28: Clinical Relevance Score AA	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 independent 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.	to be a function of the dose of irinotecan administered.'
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.	Level of evidence score: 3 IM: CTC-AE 4 PM: CTC-AE 4	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; deter-mined 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).	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.'

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Supplementary Table S3.4: ***Continued***

		*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.	
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.	Level of evidence score: 3 *28/*28: Clinical Relevance Score AA *1/*28: Clinical Relevance Score 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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: CTC-AE 4	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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: Clinical Relevance Score 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/m2 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.	Level of evidence score: 3 *1/*28: Clinical Relevance Score AA	51 patients, 26x *1/*28, 21x *1/*1, received irinotecan 180 mg/m2 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 neomycin and potential role for UGT1A1*28 genotype	Level of evidence score: 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 inducers were excluded, apart from prophylactic anti-emetics. Neomycin did not affect irinotecan toxicity or pharmacokinetics. *Clinical endpoints*	Authors' conclusion: 'It is suggested that the UGT1A1*28 genotype status could be used as a screening tool for a priori prevention of irinotecan-induced

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screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11:944-54.	(*28/*28 + *1/*28): CTC-AE 3	(*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).	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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *28/*28: Clinical Relevance Score AA[#] *1/*28: Clinical Relevance Score 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.	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

		N.B.: 5-FU dosed individually guided by adverse events.	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 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.	Level of evidence score: 3 *1/*28: Clinical Relevance Score AA *1/*6: Clinical Relevance Score A *6/*6: CTC-AE 4	81 patients, irinotecan 80 mg/m^2 on day 1 (+cisplatin) and day 8 of 3-weekly cycles, other co-medication not known; *28: 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.	Level of evidence score: 3	520 patients, 212 received irinotecan 100–125 mg/m^2 once weekly, 109x in IFLa regimen (11x *28/*28, 54x *1/*28, 44x *1/*1), 103x in IROX[b] regimen, other co-medication not known;	

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UGT1A1*28, toxicity and out-come in advanced colorectal cancer: results from Trial N9741. J Clin Oncol 2006;24 (suppl. abstr. 3520).	*28/*28: CTC-AE 4 *1/*28: CTC-AE 4	- *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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: CTC-AE 5	56 patients, 7x *28/*28, 22x *1/*28, 27x *1/*1, irinotecan 80 mg/m2 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.	Level of evidence score: 3 *28/*37: Clinical Relevance Score A *1/*28: Clinical Relevance Score A	32 patients, 30x genotyped, 3x *28/*37,18x *1/*28, 9x *1/*1, irinotecan 70-140 mg/m2 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.	

Clin Cancer Res 2005;11:4144-50.			
ref. 31 Kweekel DM et al. Ondersteuning van de chemotherapiekeuze [Support for choice of chemotherapy]. Pharm Weekblad 2005;20:685-7.	Level of evidence score: 3 *28/*28: CTC-AE 3 *1/*28: CTC-AE 3	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.	Level of evidence score: 1 *1/*28: CTC-AE 5	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.	Level of evidence score: 3 *28/*28: Clinical Relevance Score A *1/*28: Clinical Relevance Score 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.	Level of evidence score: 3	29 patients, 11% *28, oral irinotecan 100 mg/m^2 weekly, co-medication not known;	

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Pharmacogenetic profiling across the irinotecan pathway in Asian patients with cancer. Br J Clin Pharmacol 2005;59:415-24.	*28/*28: Clinical Relevance Score AA *1/*28: Clinical Relevance Score AA	The UGT1A1 genotype did not have a significant effect on kinetic parameters of irinotecan, SN-38 or SN-38G. 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.	Level of Evidence Score: 3 *28/*28: Clinical Relevance Score AA *28/*37: Clinical Relevance Score 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.	Level of evidence score: 3 *28/*28: CTC-AE 4	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.	Level of evidence score: 3 *28/*28: CTC-AE 4	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	

Br J Cancer 2004;91:678-82.	*1/*28: CTC-AE 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.	Level of evidence score: 3 *1/*28: CTC-AE 4 *28/*28: CTC-AE 5 (level of evidence score: 2)	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%). 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.	Level of evidence score: 3 *28/*28: Clinical Relevance Score A *1/*28: Clinical Relevance Score 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	Level of evidence score: 3 *28/*28: Clinical Relevance Score 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%).	

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bilirubin in irinotecan-administered Japanese patients with cancer. Clin Pharmacol Ther 2004;75:501-15.	*1/*28: Clinical Relevance Score A *6: Clinical Relevance Score A	- *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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: CTC-AE 4	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. SN-38 AUC: 336 versus 458 versus 542 ng.h/mL for *1/*1 versus *1/*28 versus *28/*28.	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 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 expo-sure.'

			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.	Level of evidence score: 3 *28/*28: Clinical Relevance Score AA *1/*28: Clinical Relevance Score 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.	Level of evidence score: 3 *28/*28: Clinical Relevance Score AA *1/*28: Clinical Relevance Score 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.	Level of evidence score: 3	20 patients, 4x *28/*28, 7x *1/*28, 9x *1/*1, irinotecan 300 mg/m2 every three weeks, co-medication not known;	SN-38 AUC versus *1/*1:

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UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43-7.	*28/*28: Clinical Relevance Score A *1/*28: Clinical Relevance Score A	*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 AUC0-24h 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 AUC0-24h increased from 205.13 to 288.61 ng.h/mL (S by 41%).	*1/*28: 141% *28/*28: 259% SN-38 AUC versus all genotypes: *1/*28: 96% *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.	Level of evidence score: 3 *28/*28: CTC-AE 4 *1/*28: CTC-AE 4 *6/*6: Clinical Relevance Score AA *1/*6: Clinical Relevance Score 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.	Level of evidence score: 2 Gilbert's syndrome: CTC-AE 4	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/m2 + 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/m2 + 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.	Level of evidence score: 0	Pharmacodynamic data: 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	

	*28/*28: CTC-AE 4	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 Camptosar (irinotecan) 30-01-20 (USA).	Level of evidence score: 0 *28/*28: CTC-AE 4	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 Camptosar (350 mg/m^2 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/m^2) 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/m^2) 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 homozygous for the wild-type allele. When administered in combination with other agents or as a single-agent, a reduction in the starting	

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		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 polymorphisms 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.

Abbreviations: *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, CTC-AE = Common Terminology Criteria for Adverse Events, DPD = dihydropyrimidine dehydrogenase, 5-FU = 5-fluorouracil, HR = hazard ratio, HRadj = adjusted hazard ratio, IM = IM other = 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, ORadj = adjusted odds ratio, PM = PM other = 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.

The clinical relevance score additionally includes the scores AA#, AA and A, since these do not exist in the CTC-AE. These regard “Positive clinical effect”, “No clinical or kinetic effect”, and “Significant kinetic effect or not clinically relevant effect”, respectively.

Supplementary Table S3.5: Dutch Pharmacogenetics Working Group (DPWG) Guideline for *UGT1A1* and irinotecan: the therapeutic recommendation and its rationale, and the kinetic and clinical consequences for each predicted UGT1A1 phenotype

Genotype/ predicted phenotype	Therapeutic recommendation	Rationale of the therapeutic recommendation	Kinetic consequences	Clinical consequences
*28/*28 [1–42]	**Start with 70% of the normal dose.** If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.	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. There is strong evidence that the *28 variant is associated with an increased frequency of serious adverse events. All 9 meta-analyses [1,5,6,11,13,24,39–41] investigating adverse events and 15 [2,8,9,12,15–20,25–27,30,34,43] of the 21 [10,14,21,23,28,31] studies found this increased risk. In addition, all 7 meta-analyses [5,6,11,13,24,39,41] and 2 studies [2,16] 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 other patients compared to all other patients. Two [6,41] of the three [11] meta-analyses that investigated grade 3-4 neutropenia showed that the risk of neutropenia was also elevated at low doses. Two [5,41] of the three [11] 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). One meta-analysis also did not find an elevated diarrhoea risk at high doses [11]. For *28, one meta-analysis 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) [1]. The most common doses used in the Netherlands are	SN-38 AUC increased by 18–159%. SN-38 metabolic clearance decreased by 61%.	**Adverse event grade 3-4 neutropenia:** Three meta-analyses found an increased risk of neutropenia (OR=3.50–5.34), similar in one meta-analysis for doses higher and lower than 150 mg/m^2 (OR 4.64 and 6.37 respectively). One of the meta-analyses also found an increased risk in White patients (OR=5.39). This meta-analysis found the same for the risk compared to *1/*1 + *1/*28 (OR=4.12 for all patients, OR=3.39 for White patients). Three other meta-analyses also found an increased risk of neutropenia versus *1/*1 + *1/*28 (OR=3.44 or RR=2.20). Two of these meta-analyses showed this risk to be dose-dependent, while the third did not (OR=27.8 or RR=7.22 for doses ≥250 mg/m^2; OR=3.22 or RR=2.00 for doses of 150–250 mg/m^2; OR=NS or 3.34 or RR=2.43 for doses <150 mg/m^2; OR=3.63 for doses >150 mg/m^2). One meta-analysis found no increase in the risk of neutropenia compared to *1/*1 and compared to *1/*1+*1/*28. One meta-analysis found an increased risk for neutropenia for *28/*28+*6/*28+*6/*6 compared to *1/*1+*1/*28+*1/*6 (OR=3.28). One meta-analysis found a trend for an increased risk of neutropenia for *28 and an increased risk for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). Results of separate studies ranged from no increase in the incidence of neutropenia to a significant increase (OR=1.97-15.3; OR_{corr}=2.89 for grade 3-4 neutropenia and 2.33 for grade 4 neutropenia (compared to *1/*1+*1/*28, increase by 50%-638%).

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		high doses (180 of 350 mg/m^2). Three [1,11,41] of the five [13,24] meta-analyses that investigated both neutropenia and diarrhoea showed that the risk of neutropenia increased more than the risk of diarrhoea. 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 [24]. Four [3,4,13,38] of the five [24] meta-analyses and eight [2,8,9,15,20,23,26,31] of the nine [18] studies did not show the *28 and/or *6 variants to be associated with increased effectiveness of the treatment. The fifth and largest meta-analysis found an increased efficacy for *1/*28+*28/*28 versus *1/*1 [24]. 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 one study showing that most *1/*28+*1/*1 tolerate the standard dose, while most *28/*28 do not [35]. 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 [35]). Moreover, one meta-analysis 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		**Adverse event grade 3–4 diarrhoea:** Five meta-analyses found an increased risk of diarrhoea (OR=1.69-5.93), but two only at doses exceeding 125 or 150 mg/m^2. Four meta-analyses found the same for the risk versus *1/*1 + *1/*28 (OR=2.04–6.25). One of the four meta-analyses found no increased risk in White patients versus *1/*1, but did find an increased risk compared to *1/*1 + *1/*28 (OR=1.62). One meta-analysis did not find an increased risk of grade 4 diarrhoea versus *1/*1 + *1/*28, not even at high doses. Results of individual studies ranged from no increase in the incidence of severe diarrhoea to a significant increase by 312%. There was one case where the patient died as a result of severe diarrhoea. **Severe toxicity (including grade 3–4 neutropenia and diarrhoea):** One meta-analysis found an increased risk of severe toxicity (OR=2.28–3.07), both for all patients (OR=2.28) and for White patients (OR=2.43), for all doses (OR=3.07) and at doses >150 mg/m^2 (OR=3.48), but not at doses <150 mg/m^2, for all tumour types (OR=2.76) and for tumours of the digestive system (OR=2.90), but not for tumours of the respiratory system. For patients with *6/*6, which leads to a comparable decrease in UGT1A1 activity, this same meta-analysis did find an effect at low doses and for tumours of the respiratory system. **Tumour response, survival:** Two meta-analyses found no difference in the therapeutic response, neither at doses exceeding 150 mg/m^2, nor at doses below 150 mg/m^2. Two meta-analyses found no difference in progression-free survival and death. The mortality rate was increased in the subgroup using doses <150 mg/m^2, but this was only based on one study and was not found in the second, larger meta-analysis. The larger meta-analysis found no

		result to be driven only by a small number of studies [24]. 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 DPWG concludes that the evidence for an increased efficacy in *28/*28 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 [37]. Dose adjustments have been calculated on the basis of SN-38 AUC or clearance in studies: The calculation was based on 6 studies with a total of 28 patients with *28/*28 [7,17,28,30,33,42]. 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		difference in the percentage of patients with one or more cycles with reduced irinotecan dose for *28/*28. One meta-analysis found no difference in tumour response for *1/*28+*28/*28. One meta-analysis found an improved tumour response for *1/*28+*28/*28 (OR=1.20 for all patients, OR=1.23 for White patients), but this difference was only significant in the 4 retrospective studies with a total of 538 patients, not in the 12 prospective studies with 1,292 patients. Results of individual studies ranged from no effect of genotype on tumour response, time to progression and overall survival to an association between genotype and improved tumour response. The risk of progression or progressive/stable disease was reduced (OR 0.19 and 0.32 respectively). One study involving 5 *28/*28 at 67% of the standard initial dose and 65 *1/*1+*1/*28 at the standard initial dose (180 mg/m^2) found that the incidence of clinical effects grade 3–4 was still 9.7 times higher for *28/*28, whilst the effectiveness was reduced (reduction in complete or partial response by 74%, reduction in the incidence of disease control (response or stable disease) by 57% and a reduction in the progression-free survival by the number of *28 alleles). However, one cannot rule out that this was caused by subsequently attempting a dose increase, with the maximum dose used for *28/*28 being 81% of the maximum dose for *1/*1 and 88% of the maximum dose for *1/*28. In the aforementioned study, the average maximum tolerated dose for *28/*28 was 76% of the dose for *1/*1+*1/*28 (156 versus 206 mg/m^2) and the maximum dose that was tolerated by the largest group of patients with the genotype (40%) for *28/*28 was 67% of the dose for *1/*1+*1/*28 (120 versus 180 mg/m^2).

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		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, one study 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 [35]. In this study, reduction of the initial dose with 33% for *28/*28 did not result in toxicity and efficacy that was 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.		
*1/*28 [1–7,9,10, 12–22,24, 26–34,36, 38,40–46]	**NO action is needed for this gene-drug interaction.**	For *1/*28, a similar amount of evidence is present as for *28/*28. 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 [1,5,6,13,24,40,41]. However, *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 is confirmed by a study showing that most *1/*28+*1/*1 tolerate the standard dose [35] and by the negligible dose adjustment calculated for *1/*28 compared to all	SN-38 AUC increased by 4.6–41%. SN-38 metabolic clearance decreased by 37%.	**Adverse event grade 3-4 neutropenia:** Four meta-analyses found an increased risk of neutropenia (RR=1.43, OR=1.71–1.91), two both at low and high doses and a third both for all patients (OR=1.71) and for White patients (OR=1.86). One meta-analysis found no increased risk of neutropenia. One meta-analysis found a trend for an increased risk of neutropenia for *28 and an increased risk for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). Results of separate studies ranged from no increase in the incidence of neutropenia to a significant increase

		genotypes (see below). This means that dose reduction for *1/*28 would lead in suboptimal doses for this patient group. Therefore, the DPWG concludes that a gene-drug interaction is present, but that therapy adjustment is neither required nor advisable. Dose adjustments have been calculated on the basis of SN-38 AUC or clearance in studies: A total of 112 patients with *1/*28 were present in the 6 studies used for dose calculation [7,17,28,30,33,42]. 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 patients at this time.		(OR=1.93–3.47; increase by 12.5–313%). **Adverse event grade 3-4 diarrhoea:** Three meta-analyses found an increased risk of diarrhoea (OR=1.45–1.73), but one only at doses ≥125 mg/m^2 (OR=1.92). The other meta-analysis did find an increased risk for all patients (OR=1.56), but not for White patients. Two other meta-analyses found no difference, one only a trend for a higher risk at doses >150 mg/m^2. Results of individual studies ranged from no increase in the incidence of diarrhoea to a significant increase by 94%. There were two cases where the patient died as a result of severe diarrhoea in combination with haematological toxicity. **Severe toxicity (including grade 3-4 neutropenia and diarrhoea):** One meta-analysis found an increased risk of severe toxicity (OR=1.60–1.77), both for all patients (OR=1.60) and for White patients (OR=1.59), for all doses (OR=1.77) and at doses >150 mg/m^2 (OR=1.81), but not at doses <150 mg/m^2, for all tumour types (OR=1.68) and for tumours of the digestive system (OR=1.73), but not for tumours of the respiratory system. **Tumour response, time to progression and overall survival**: four meta-analyses and individual studies found no difference. One of these four meta-analyses found a trend for an increase in the percentage of patients with one or more cycles of reduced irinotecan dose for *1/*28. One meta-analysis found an improved tumour response for *1/*28+*28/*28 (OR=1.20 for all patients, OR=1.23 for White patients), but this difference was only significant in the 4 retrospective studies with a total of 538 patients, not in the 12 prospective studies

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Supplementary Table S3.5: ***Continued***

				with 1,292 patients.
PM other [1,5,7,12, 13,17,28–30,33,34, 39,40,42, 43]	**Start with 70% of the normal dose.** If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.	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. There is strong evidence that the *6 and/or *28 variants are associated with an increased frequency of serious adverse events. All 4 meta-analyses [1,5,13,39] investigating adverse events and 5 [12,17,30,34,43] of the 6 [28] studies found this increased risk. In addition, all 3 meta-analyses [5,13,39] and the only studies [43] investigating the effect of *6/*6 and/or *6/*28 and/or *28/*28 compared with all other genotypes, found that this risk was also increased for PM other and/or *28/*28 patients compared to all other patients. One meta-analysis 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) [5]. For *6, one meta-analysis found the risk of severe toxicity (including neutropenia and diarrhoea) to be increased at both high and low doses, with the ORs being higher at low doses [1]. The most common doses used in the Netherlands are high doses (180 of 350 mg/m^2). The only effectiveness meta-analysis [13] did not show the *6 variant to be associated with increased effectiveness of the treatment, but the only effectiveness study [43] suggested a decreased effectiveness for *6/*6. Taking into account the lack of sufficient evidence for *28, which has comparable kinetic and clinical	The information on kinetic consequences has mainly been derived from the *28/*28 genotype which encodes the PM phenotype but for which there are separate pharmacogenetic guidelines. ***28/*28:** SN-38 AUC increased by 18-159%. SN-38 metabolic clearance decreased by 61%. **PM + *28/*28 (*6/*6 + *6/*28 + *28/*28):** SN-38 AUC increased by 140%. ***6/*6:** SN-38 AUC increased by 76%.	**Adverse event grade 3-4 neutropenia:** *6/*6: Two meta-analyses found an increased risk of neutropenia (OR=3.03–3.28). Another meta-analysis found no increased risk of neutropenia compared to *1/*1, but did find an increased risk compared to *1/*1+*1/*6 (OR=5.00). A third meta-analysis found a trend towards an increased risk of neutropenia for *6. One study found a 2.8-fold increased percentage of patients with grade 4 neutropenia compared to *1/*1+*1/*6 (from 24% to 67%). PM + *28/*28 (*6/*6 + *6/*28 + *28/*28): One meta-analysis found an increased risk of neutropenia (OR=3.28). A second meta-analysis found an increased risk of neutropenia for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). One study found a 5.7-fold increased incidence of neutropenia (from 14% to 80%). **Adverse event grade 3-4 diarrhoea:** *6/*6: Three meta-analyses found an increased risk of diarrhoea (OR=3.54–17.6). One of these meta-analyses also found an increased risk compared to *1/*1+*1/*6 (OR=5.26). One study found no association. PM + *28/*28: One study found no association with the incidence of diarrhoea. **Severe toxicity (including grade 3-4 neutropenia and diarrhoea):**

		effects as *6, the DPWG concludes that the evidence for an increased efficacy in PM other patients is not convincing enough to refrain from recommending a dose reduction in these patients. 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, the same dose reduction as for *28/*28 is recommended for PM other [12].		*6/*6: One meta-analysis including only Asian studies found an increased risk of severe toxicity (OR=3.16–-3.21) for all doses (OR=3.17), at doses >150 mg/m^2 (OR=2.91) and at doses <150 mg/m^2 (OR=9.42), for all tumour types (OR=3.21), for tumours of the digestive system (OR=3.00) and for tumours of the respiratory system (OR=18.2; based on only 1 study). **Tumour response, survival:** *6/*6: One meta-analysis found no difference in tumour response for *1/*6+*6/*6. One study found that the percentage of responders decreased from 50% to 0% and also found decreased progression-free and overall survival compared to *1/*6+*6/*6.
IM other [1,7,12,13, 17,28–30, 33,34,40, 42,43]	**NO action is needed for this gene-drug interaction.**	For IM other and *1/*28, a similar amount of evidence is present as for PM other and *28/*28. All three meta-analyses that investigated the effect of *1/*6 and/or *1/*28 found an elevated frequency of serious adverse events for *1/*6 and/or *1/*28 versus *1/*1 [1,13,40]. However, *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 group is larger than the *1/*1 group. This is confirmed by a study showing that most *1/*28+*1/*1 tolerate the standard dose [35] and by the negligible dose adjustment calculated for *1/*28 compared to all genotypes (see the rationale for *1/*28). This means that dose reduction for *1/*28 would lead in suboptimal doses for this patient group. Because the kinetic and clinical effects of *6	The information on kinetic consequences has mainly been derived from the *1/*28 genotype which encodes the IM phenotype but for which there are separate pharmacogenetic guidelines. ***1/*28:** SN-38 AUC increased by 4.6-41%. SN-38 metabolic clearance	**Adverse event grade 3–4 neutropenia:** *1/*6: One meta-analysis found an increased risk of neutropenia (OR=1.95). Another meta-analysis found no increased risk. A third meta-analysis found a trend for an increased neutropenia risk for *6. IM + *1/*28 (*1/*6 + *1/*28): One meta-analysis found an increased risk of neutropenia for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). One study found a 1.7-fold increased incidence of neutropenia (from 14% to 24%). **Adverse event grade 3–4 diarrhoea:** *1/*6: Two meta-analyses found an increased risk of diarrhoea (OR=1.98–4.36). IM + *1/*28 (*1/*6 + *1/*28): One study found no

Supplementary Table S3.5 continues on next page.

Supplementary Table S3.5: ***Continued***

		and *28 are comparable, the same is true for IM other. Therefore, the DPWG concludes that a gene-drug interaction is present, but that therapy adjustment is neither required nor advisable.	decreased by 37%. **IM + *1/*28 (*1/*6 + *1/*28):** SN-38 AUC increased by 40%. ***1/*6:** SN-38 AUC increased by 11%.	association with the incidence of diarrhoea. **Severe toxicity (including grade 3-4 neutropenia and diarrhoea):** *1/*6: One meta-analysis including only Asian studies found an increased risk of severe toxicity (OR=1.75–2.08) for all doses (OR=2.08), at doses >150 mg/m^2 (OR=1.82) and at doses <150 mg/m^2 (OR=3.49), for tumours of all types (OR=1.75), for tumours of the digestive system (OR=1.66) and for tumours of the respiratory system (OR=12.0; based on only 1 study). **Tumour response, time to progression and overall survival:** One meta-analysis found no difference in tumour response for *1/*6+*6/*6.

*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, IM = IM other = 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, PM = PM other = 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, SN-38 = active metabolite of irinotecan (7-ethyl-10-hydroxycamptothecin), UGT = uridine diphosphate glucuronosyltransferase, UGT1A1*1 = TA6 = [A(TA)6TAA] = wild-type, UGT1A1*28 = TA7 = [A(TA)7TAA] (reduced UGT1A1 activity), UGT1A1*6 = gene variant in Asians, reduced activity, comparable to *28.

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Supplementary Table S3.6: Suggested clinical decision support texts for health care professionals for irinotecan

***UGT1A1 *28/*28*: IRINOTECAN**

Pharmacist and physician text
Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the normal dose
  If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Background information
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.

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

For more information about the UGT1A1 *28/*28 genotype, see the general background information about UGT1A1 on the KNMP Kennisbank (search for UGT1A1).

Clinical consequences:
Adverse event grade 3–4 neutropenia: Three meta-analyses found an increased risk of neutropenia (OR = 3.50–5.34), similar in one meta-analysis for doses higher and lower than 150 mg/m^2 (OR 4.64 and 6.37 respectively). One of the meta-analyses also found an increased risk in White patients (OR=5.39). This meta-analysis found the same for the risk compared to *1/*1 + *1/*28 (OR=4.12 for all patients, OR=3.39 for White patients). Three other meta-analyses also found an increased risk of neutropenia versus *1/*1 + *1/*28 (OR=3.44 or RR=2.20). Two of these meta-analyses showed this risk to be dose-dependent, while the third did not (OR=27.8 or RR=7.22 for doses ≥250 mg/m^2; OR=3.22 or RR=2.00 for doses of 150–250 mg/m^2; OR=NS or 3.34 or RR=2.43 for doses <150 mg/m^2; OR=3.63 for doses >150 mg/m^2). One meta-analysis found no increase in the risk of neutropenia compared to *1/*1 and compared to *1/*1+*1/*28. One meta-analysis found an increased risk for neutropenia for *28/*28+*6/*28+*6/*6 compared to *1/*1+*1/*28+*1/*6 (OR=3.28). One meta-analysis found a trend for an increased risk of neutropenia for *28 and an increased risk for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). Results of separate studies ranged from no increase in the incidence of neutropenia to a significant increase (OR=1.97–15.3; OR_{corr}=2.89 for grade 3–4 neutropenia and 2.33 for grade 4 neutropenia (compared to *1/*1+*1/*28), increase by 50–638%).

Adverse event grade 3–4 diarrhoea: Five meta-analyses found an increased risk of diarrhoea (OR=1.69–5.93), but two only at doses exceeding 125 or 150 mg/m^2. Four meta-analyses found the same for the risk versus *1/*1 + *1/*28 (OR=2.04–6.25). One of the four meta-analyses found no increased risk in White patients versus *1/*1, but did find an increased risk compared to *1/*1 + *1/*28 (OR=1.62). One meta-analysis did not find an increased risk of grade 4 diarrhoea versus *1/*1 + *1/*28, not even at high doses. Results of individual studies ranged from no increase in the incidence of severe diarrhoea to a significant increase by 312%. There was one case where the patient died as a result of severe diarrhoea.

Severe toxicity (including grade 3–4 neutropenia and diarrhoea): One meta-analysis found an increased risk of severe toxicity (OR=2.28–3.07), both for all patients (OR=2.28) and for White patients (OR=2.43),

for all doses (OR=3.07) and at doses >150 mg/m^2 (OR=3.48), but not at doses <150 mg/m^2, for all tumour types (OR=2.76) and for tumours of the digestive system (OR=2.90), but not for tumours of the respiratory system. For patients with *6/*6, which leads to a comparable decrease in UGT1A1 activity, this same meta-analysis did find an effect at low doses and for tumours of the respiratory system.

Tumour response, survival etc.: Two meta-analyses found no difference in the therapeutic response, neither at doses exceeding 150 mg/m^2, nor at doses below 150 mg/m^2. Two meta-analyses found no difference in progression-free survival and death. The mortality rate was increased in the subgroup using doses <150 mg/m^2, but this was only based on one study and was not found in the second, larger meta-analysis. The larger meta-analysis found no difference in the percentage of patients with one or more cycles with reduced irinotecan dose for *28/*28. One meta-analysis found no difference in tumour response for *1/*28+*28/*28. One meta-analysis found an improved tumour response for *1/*28+*28/*28 (OR=1.20 for all patients, OR=1.23 for White patients), but this difference was only significant in the 4 retrospective studies with a total of 538 patients, not in the 12 prospective studies with 1,292 patients.

Results of individual studies ranged from no effect of genotype on tumour response, time to progression and overall survival to an association between genotype and improved tumour response. The risk of progression or progressive/stable disease was reduced (OR 0.19 and 0.32 respectively).

One study involving 5 *28/*28 at 67% of the standard initial dose and 65 *1/*1+*1/*28 at the standard initial dose (180 mg/m^2) found that the incidence of clinical effects grade 3–4 was still 9.7 times higher for *28/*28, whilst the effectiveness was reduced (reduction in complete or partial response by 74%, reduction in the incidence of disease control (response or stable disease) by 57% and a reduction in the progression-free survival by the number of *28 alleles). However, one cannot rule out that this was caused by subsequently attempting a dose increase, with the maximum dose used for *28/*28 being 81% of the maximum dose for *1/*1 and 88% of the maximum dose for *1/*28.

In the aforementioned study, the average maximum tolerated dose for *28/*28 was 76% of the dose for *1/*1+*1/*28 (156 versus 206 mg/m^2) and the maximum dose that was tolerated by the largest group of patients with the genotype (40%) for *28/*28 was 67% of the dose for *1/*1+*1/*28 (120 versus 180 mg/m^2).

Kinetic consequences:
SN-38 AUC increased by 18–159%.
SN-38 metabolic clearance decreased by 61%.

Literature

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.
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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.
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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.
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25. 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.
26. 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).
27. 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.
28. Kweekel DM, et al. Ondersteuning van de chemotherapiekeuze. Pharm Weekblad 2005;20:685–7.
29. 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.

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37. Innocenti F, et al. Genetic variants in the UDP-glucuronosyl-transferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22:1382–8.
38. 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.
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40. Iyer L, et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43–7.
41. Ando Y, et al. Polymorphisms of UDP-glucuronosyl-transferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921–6.
42. Wasserman E, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049–51.
43. SmPCs Campto (NL) and Camptosar (USA).

Preferably implemented as a lookup text only, not as a popup text:

***UGT1A1 *1/*28*: IRINOTECAN**

Pharmacist and physician text
NO action is needed for this gene-drug interaction.

This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

Background information
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.

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

For more information about the UGT1A1 *1/*28 genotype, see the general background information about UGT1A1 on the KNMP Kennisbank (search for UGT1A1).

Clinical consequences:
Adverse event grade 3–4 neutropenia: Four meta-analyses found an increased risk of neutropenia (RR=1.43, OR=1.71–1.91), two both at low and high doses and a third both for all patients (OR=1.71) and for White patients (OR=1.86). One meta-analysis found no increased risk of neutropenia. One meta-analysis found a trend for an increased risk of neutropenia for *28 and an increased risk for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). Results of separate studies ranged from no increase in the incidence of neutropenia to a significant increase (OR=1.93–3.47; increase by 12.5–313%).

Adverse event grade 3–4 diarrhoea: Three meta-analyses found an increased risk of diarrhoea (OR=1.45–1.73), but one only at doses ≥125 mg/m^2 (OR=1.92). The other meta-analysis did find an increased risk for all patients (OR=1.56), but not for White patients. Two other meta-analyses found no difference, one only a trend for a higher risk at doses >150 mg/m^2. Results of individual studies ranged from no increase in the incidence of diarrhoea to a significant increase by 94%. There were two cases where the patient died as a result of severe diarrhoea in combination with haematological toxicity.

Severe toxicity (including grade 3–4 neutropenia and diarrhoea): One meta-analysis found an increased risk of severe toxicity (OR=1.60–1.77), both for all patients (OR=1.60) and for White patients (OR=1.59), for all doses (OR=1.77) and at doses >150 mg/m^2 (OR=1.81), but not at doses <150 mg/m^2, for all tumour types (OR=1.68) and for tumours of the digestive system (OR=1.73), but not for tumours of the respiratory system.

Tumour response, time to progression and overall survival: four meta-analyses and individual studies found no difference. One of these four meta-analyses found a trend for an increase in the percentage of patients with one or more cycles of reduced irinotecan dose for *1/*28. One meta-analysis found an improved tumour response for *1/*28+*28/*28 (OR=1.20 for all patients, OR=1.23 for White patients), but this difference was only significant in the 4 retrospective studies with a total of 538 patients, not in the 12 prospective studies with 1,292 patients.

Kinetic consequences:
SN-38 AUC increased by 4.6–41%.
SN-38 metabolic clearance decreased by 37%.

Literature

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.
2. Tejpar S, et al. Clinical and pharmacogenetic determinants of 5-fluorouracyl/ leucovorin/irinotecan toxicity: results of the PETACC-3 trial. Eur J Cancer. 2018;99:66–77.
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40. Wasserman E, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049–51.

***UGT1A1* PM OTHER: IRINOTECAN**

Pharmacist and physician text
Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the normal dose
  If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Background information
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.

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

For more information about the UGT1A1 PM other phenotype, see the general background information about UGT1A1 on the KNMP Kennisbank (search for UGT1A1).

Clinical consequences:
Adverse event grade 3-4 neutropenia:
*6/*6: Two meta-analyses found an increased risk of neutropenia (OR=3.03–3.28). Another meta-analysis found no increased risk of neutropenia compared to *1/*1, but did find an increased risk compared to *1/*1+*1/*6 (OR=5.00). A third meta-analysis found a trend towards an increased risk of neutropenia for *6. One study found a 2.8-fold increased percentage of patients with grade 4 neutropenia compared to *1/*1+*1/*6 (from 24% to 67%).

PM + *28/*28 (*6/*6 + *6/*28 + *28/*28): One meta-analysis found an increased risk of neutropenia (OR=3.28). A second meta-analysis found an increased risk of neutropenia for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). One study found a 5.7-fold increased incidence of neutropenia (from 14% to 80%).

Adverse event grade 3–4 diarrhoea:
*6/*6: Three meta-analyses found an increased risk of diarrhoea (OR=3.54–17.6). One of these meta-analyses also found an increased risk compared to *1/*1+*1/*6 (OR=5.26). One study found no association. PM + *28/*28: One study found no association with the incidence of diarrhoea.

Severe toxicity (including grade 3–4 neutropenia and diarrhoea):
*6/*6: One meta-analysis including only Asian studies found an increased risk of severe toxicity (OR=3.16–3.21) for all doses (OR=3.17), at doses >150 mg/m^2 (OR=2.91) and at doses <150 mg/m^2 (OR=9.42), for all tumour types (OR=3.21), for tumours of the digestive system (OR = 3.00) and for tumours of the respiratory system (OR=18.2; based on only 1 study).

Tumour response, survival etc.:
*6/*6: One meta-analysis found no difference in tumour response for *1/*6+*6/*6.
ne study found that the percentage of responders decreased from 50% to 0% and also found decreased progression-free and overall survival compared to *1/*6+*6/*6.

Kinetic consequences:
The information on kinetic consequences has mainly been derived from the *28/*28 genotype which encodes the PM phenotype but for which there are separate pharmacogenetic guidelines.

*28/*28: SN-38 AUC increased by 18–159%. SN-38 metabolic clearance decreased by 61%.
PM + *28/*28 (*6/*6 + *6/*28 + *28/*28): SN-38 AUC increased by 140%.
*6/*6: SN-38 AUC increased by 76%.

Literature

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.
2. 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;79:1109–17.
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15. Ando Y, et al. Polymorphisms of UDP-glucuronosyl-transferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921–6.

Preferably implemented as a lookup text only, not as a popup text:

UGT1A1 IM OTHER: IRINOTECAN

Pharmacist and physician text

NO action is needed for this gene-drug interaction.

This genetic variation (IM) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

Background information

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.

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

For more information about the UGT1A1 IM other phenotype, see the general background information about UGT1A1 on the KNMP Kennisbank (search for UGT1A1).

Clinical consequences:

Adverse event grade 3-4 neutropenia:

*1/*6: One meta-analysis found an increased risk of neutropenia (OR=1.95). Another meta-analysis found no increased risk. A third meta-analysis found a trend for an increased neutropenia risk for *6.

IM + *1/*28 (*1/*6 + *1/*28): One meta-analysis found an increased risk of neutropenia for *28+*6 (OR_G=2.55, which means that patients with neutropenia had a 155% higher frequency of *28 and *6 than patients without neutropenia). One study found a 1.7-fold increased incidence of neutropenia (from 14% to 24%).

Adverse event grade 3–4 diarrhoea:

*1/*6: Two meta-analyses found an increased risk of diarrhoea (OR=1.98–4.36).

IM + *1/*28 (*1/*6 + *1/*28): One study found no association with the incidence of diarrhoea.

Severe toxicity (including grade 3–4 neutropenia and diarrhoea):

*1/*6: One meta-analysis including only Asian studies found an increased risk of severe toxicity (OR=1.75–2.08) for all doses (OR=2.08), at doses >150 mg/m^2 (OR=1.82) and at doses <150 mg/m^2 (OR=3.49), for tumours of all types (OR=1.75), for tumours of the digestive system (OR=1.66) and for tumours of the respiratory system (OR=12.0; based on only 1 study).

Tumour response, time to progression and overall survival:

One meta-analysis found no difference in tumour response for *1/*6+*6/*6.

Kinetic consequences:

The information on kinetic consequences has mainly been derived from the *1/*28 genotype which encodes the IM phenotype but for which there are separate pharmacogenetic guidelines.

*1/*28: SN-38 AUC increased by 4.6–41%. SN-38 metabolic clearance decreased by 37%.

IM + *1/*28 (*1/*6 + *1/*28): SN-38 AUC increased by 40%.

*1/*6: SN-38 AUC increased by 11%.

Literature

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.
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Supplementary Table S3.7: Based on the criteria and corresponding scores given by the Dutch Pharmacogenetics Working Group (DPWG), the Clinical Implication Score for irinotecan is "Essential"

Table S3.7a: 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 S3.7b: 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)	++	++[1]
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	+++	+++[2]
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥3		
• 100<NNG≤1000	+	
• 10<NNG≤100	++	++[3]
• NNG≤10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+[4]
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

[1] 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).

[2] 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).

[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).

[4] 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).