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Review

Pre-therapeutic *UGT1A1* genotyping to reduce the risk of irinotecan-induced severe toxicity: Ready for prime time

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Abstract ***Background:*** Pre-therapeutic *UGT1A1* genotyping is not yet routinely performed in most hospitals in patients starting irinotecan chemotherapy. The aim of this position paper was to evaluate the available evidence and to assess the potential value of genotyping of *UGT1A1*28* and *UGT1A1*6* in patients before starting treatment with irinotecan to reduce the risk of severe toxicity.
Methods: The literature was selected and assessed based on five pre-specified criteria: 1) the level of evidence for associations between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity, 2) clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*, 3) safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms, 4) availability of specific dose recommendations for irinotecan in carriers of *UGT1A1* polymorphisms, 5) evidence of cost benefits of pre-therapeutic genotyping of *UGT1A1*.
Results: On all five criteria, study results were favourable for pre-therapeutic genotyping of *UGT1A1*. A high level of evidence (level I) was found for a higher incidence of irinotecan-induced severe toxicity in homozygous carriers of *UGT1A1*28* or *UGT1A1*6*. The clinical validity and utility of this genetic test proved to be acceptable. Dose-finding studies showed a lower maximum tolerated dose in homozygous variant allele carriers, and most of the drug labels and guidelines recommend a dose reduction of 25–30% in these patients. In addition, pre-therapeutic genotyping of *UGT1A1* is likely to save costs.

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Conclusion: Pre-therapeutic genotyping of *UGT1A1* in patients initiating treatment with irinotecan improves patient safety, is likely to be cost-saving, and should, therefore, become standard of care.

1. Introduction

Irinotecan is a commonly applied anticancer drug that frequently leads to complications such as severe delayed diarrhoea and neutropenia. Irinotecan is registered for the first-line treatment of pancreatic cancer and the second-line treatment of colorectal cancer and is also used in other tumour types, such as 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 [1,2].

Irinotecan is a prodrug that is activated via carboxylesterases in the liver and blood to SN38, which in turn is glucuronidated in the liver and intestines into SN38-glucuronide (SN38-G) by UDP-glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 is the main enzyme responsible for the inactivation of SN38 [3].

Several genetic variants within the *UGT1A1* gene are known to be associated with reduced UGT1A1 enzyme activity and, therefore, with an increased risk for irinotecan-related severe toxicity [4,5]. The most well-characterised *UGT1A1* genetic variants are *UGT1A1*28* and *UGT1A1*6*. *UGT1A1*28* is a common tandem-repeat polymorphism in the promotor region of the *UGT1A1* gene that leads to reduced enzyme activity, which is also known as Gilbert's syndrome [6,7]. Homozygous carriers of these variants have a decreased UGT1A1 expression of up to 70% [7]. The polymorphism *UGT1A1*6* is a missense mutation and reduces UGT1A1 enzyme activity to an extent that is comparable to the effect of *UGT1A1*28* [8,9]. The *UGT1A1*28* polymorphism is highly prevalent in the African, Latino, and European population, with a minor allele frequency (MAF) ranging from 32% to 40%, whereas this polymorphism occurs less frequently in the East-Asian population (MAF 12%) and does not occur in the South-Asian population [10]. In contrast, the *UGT1A1*6* polymorphism has the highest MAF in the East-Asian population, i.e. 15%, compared with 0–5% in all other populations [10]. In the Chinese and Japanese population also a combined occurrence of *UGT1A1*6* and *UGT1A1*28* was reported with an incidence ranging from 3 to 8% [8,11,12]. A considerable amount of the literature has been published on the association between *UGT1A1* polymorphism and severe toxicity of irinotecan, but, so far, *UGT1A1* genotyping is not being routinely applied. Therefore, the aim of this position paper was to evaluate the available evidence and to assess the potential value of pre-therapeutic genotyping of *UGT1A1*28* and *UGT1A1*6* in patients indicated for treatment with irinotecan. The outcomes of this study are relevant for oncologists who prescribe irinotecan in daily practice and for their patients.

2. Methods

A literature search was conducted to compile the available evidence on *UGT1A1* genotyping in patients treated with irinotecan. We searched PubMed until March 2020 without any limitations on publication year using the following search terms: "irinotecan", "CPT-11", "pharmacogenetics", "cost-effectiveness", "cost-analysis", "UGT1A1", "UGT1A1*6", and "UGT1A1*28". Reference lists in original articles and review articles were manually searched to identify additional potentially relevant publications. In addition, we screened all the available drug labels and guidelines on irinotecan provided on PharmGKB [13].

Publications were included if they reported on at least one of the following subjects: 1) the association between irinotecan-related toxicity and carriership of *UGT1A1*6* or *UGT1A1*28*; 2) *UGT1A1* genotype-guided dose-finding studies for irinotecan; 3) dose recommendations on drug labels or in guidelines for the administration of irinotecan in carriers of *UGT1A1*6* or *UGT1A1*28*; or 4) cost-evaluation of pre-therapeutic *UGT1A1*6* or *UGT1A1*28* genotyping. Publications reporting on liposomal irinotecan were excluded.

To assess the available evidence for pre-therapeutic genotyping of *UGT1A1* in patients treated with irinotecan in a structured and objective manner, data were assessed based on five main criteria, in accordance with standardised guidelines [14–16] on assessing the clinical validity and clinical utility of pharmacogenetic testing.

1. The level of evidence for the association between UGT1A1 polymorphisms and irinotecan-induced severe toxicity

The following toxicity end-points were assessed: grade ≥III neutropenia, grade ≥III diarrhoea, febrile neutropenia, irinotecan-related hospital admissions, and death. If available, odds ratios or relative risks were reported for each end-point. The level of evidence for each end-point was assessed in accordance with the standard operating procedures of the European Society

of Medical Oncology [17]. The levels range from V to I, in which level I is the highest level of evidence.

2. Clinical validity and utility of pre-therapeutic genotyping of UGT1A1

The clinical validity of pre-therapeutic genotyping of *UGT1A1* describes the accuracy of this genetic test to identify a patient's risk to develop severe toxicity [16]. The clinical validity was assessed by calculating the sensitivity, the specificity, and the positive and negative predictive value. In general, a low sensitivity may be expected because other (genetic) factors are also known to be predictive for irinotecan-induced toxicity and not all toxicity may be attributed to only one single polymorphism.

The clinical utility of pre-therapeutic genotyping of *UGT1A1* describes the ability of genotyping to prevent severe toxicity through differentiation in treatment based on the genotyping results. The clinical utility was assessed by calculating the number needed to treat (NNT) (i.e. to apply a dose reduction) and the number needed to genotype (NNG) [14].

Clinical validity and utility parameters were calculated for both *UGT1A1*6* and *UGT1A1*28* for the most important adverse events, that is, grade ≥III diarrhoea and neutropenia in a recessive genetic model: homozygous versus heterozygous plus wild type.

Because there are no clear cut-off values for deciding whether pre-therapeutic genotyping of *UGT1A1* is clinically valid and utile, values were also compared with those of the genotype test recently recommended by the European Medicines Agency for the pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines [18]. A position paper by Lunenburg et al. [19] presented the clinical validity and utility parameters for this genotype test; these parameters were calculated for *DPYD*2A* and c.2846A > T for grade ≥III toxicity.

3. Safety and tolerability of irinotecan in carriers of UGT1A1 polymorphisms

All available *UGT1A1* genotype-guided dose-finding studies for irinotecan were collected. To compare the outcomes of all the identified studies, relative dose intensities were calculated per study and genotype category and reported in a forest plot. The relative dose intensity was calculated by dividing the recommended dose or maximum tolerable dose reported in each study by the standard conventional dose of irinotecan conform the treatment schedule used in each study, multiplied by 100%.

4. Availability of specific dose recommendations for irinotecan in carriers of UGT1A1 polymorphisms

Specific dose recommendations per *UGT1A1* genotype category are necessary to provide guidance for oncologists in applying *UGT1A1* genotype-guided dosing. Drug labels and clinical guidelines were screened for the presence of specific dose recommendations per *UGT1A1* genotype category.

5. Evidence of cost benefits of pre-therapeutic genotyping of UGT1A1

The implementation of pre-therapeutic *UGT1A1* genotyping will increase treatment costs because of the extra costs for genotyping, but it might also be cost-saving because of the reduction of severe irinotecan-induced toxicity and hospitalisation. All the available cost-analysis publications on pre-therapeutic *UGT1A1* genotyping were assessed.

3. Results

Based on the selection criteria, a total of 41 publications, four drug labels, and three guidelines were included, specifically resulting in a total of 23, 1, 12, 7, and 5 included publications for criteria 1–5, respectively.

1] Level of evidence for the association between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity

A considerable amount of the literature has been published on the increased risk for irinotecan-related toxicity in homozygous *UGT1A1*28* variant allele carriers; this increased risk has been demonstrated in case reports on several [20], sometimes even lethal adverse events [21,22], in multiple retrospective and prospective genetic association studies [23–25] and also in several meta-analyses [26–30]. A similar increased risk for irinotecan-related toxicity in homozygous *UGT1A1*6* variant allele carriers has been reported in several genetic association studies [31–33] and several meta-analyses [34–38].

Carriership of a *UGT1A1* polymorphism was highly associated with grade ≥III neutropenia and grade ≥III diarrhoea (level of evidence I). For *UGT1A1*28*, the largest effect size was seen in homozygous carriers compared with heterozygous and wild-type patients (recessive model): four [26–29] of five [26–29,34] meta-analyses showed a two-to four-fold increased risk of grade ≥III neutropenia. In all three meta-analyses on *UGT1A1*6,* a similar increased neutropenia risk was observed [34,35,37]. For *UGT1A1*28,* a two- to six-fold increased risk of grade ≥III diarrhoea was observed in four [28–30,34] of five [26,28–30,34] meta-analyses; in addition, the effect size seemed larger in patients treated at medium or higher doses of irinotecan (>125 mg/m^2). In three meta-analyses reporting on *UGT1A1*6* and severe diarrhoea, homozygotes had a three- to four-fold increased risk compared with wild-type patients [36,38] and a four-fold increased risk compared with heterozygous and wild-type patients [34]. A more

detailed description of all meta-analyses of studies on the association of *UGT1A1* polymorphisms and grade ≥III neutropenia and diarrhoea is provided in Tables 1a and 1b.

Level III and IV evidence was available for the association between *UGT1A1*28* and febrile neutropenia [39–42]. One study reporting on the administration of low doses of irinotecan (50–60 mg/m^2) could not

Table 1a
Association between irinotecan-related severe neutropenia and *UGT1A1* polymorphism.

Group	n total	Ethnicity	Polymorphism	Association with irinotecan grade ≥ III neutropenia				
				Comparison	n	Dose (mg/m^2)	OR	95% CI
Hoskins et al., 2007 [26]	821	Caucasian	*28	HO vs HE + WT	229	100–125	1.80	0.37–8.84
					410	180	3.22	1.52–6.81
					184	200–350	27.8	4.0–195
Hu et al., 2010 [27]	1998	Mainly Caucasian	28	HO vs HE + WT	1998	80–350	2.20[a]	1.82–2.66
					300	<150	2.43[a]	1.34–4.39
					1481	150–250	2.00[a]	1.62–2.47
					217	≥250	7.22[a]	3.10–16.78
				HE vs WT	1738	80–350	1.43[a]	1.16–1.77
					270	<150	2.94[a]	1.36–6.35
					1288	150–250	1.29[a]	1.04–1.62
					180	≥250	2.65[a]	0.70–9.94
Liu et al., 2014 [28]	2015	Caucasian	*28	HO vs HE + WT	2015	80–350	3.44	2.45–4.82
					704	<150	3.63	2.02–6.53
					1311	≥150	3.34	2.21–5.05
				HO vs WT	1095	80–350	4.79	3.28–7.01
					331	<150	6.37	2.69–10.71
					764	≥150	4.64	2.88–7.17
				HE vs WT	1819	80–350	1.90	1.44–2.51
					630	<150	2.01	1.21–3.34
					1189	≥150	1.85	1.32–2.58
Han et al., 2014 [35]	994	Asian	*6	HO vs HE + WT	984	50–350	3.28	1.89–5.69
				HO + HE vs WT	994	50–350	1.54	1.18–2.04
			*6/*28	HO+*6/*28 vs HE + WT	923	50–350	3.28	2.15–4.98
Cheng et al., 2014 [36]	1027	Asian	*6	HO vs WT	576	30–180	4.44	2.42–8.14
					116	<150	9.64	2.05–45.28
					460	≥150	3.95	2.05–7.64
				HE vs WT	933	30–180	1.98	1.45–2.71
					249	<150	4.42	2.27–8.59
					684	≥150	1.55	1.08–2.22
Liu et al., 2017 [29]	6087	Asian and Caucasian	*28	HO vs HE + WT	3668	60–350	4.12	2.36–7.20
				HO + HE vs WT	5232	60–350	2.15	1.71–2.70
				HO vs WT	3575	60–350	5.34	3.05–9.33
				HE vs WT	3948	60–350	1.71	1.41–2.08
Chen et al., 2017 [34]	577	Asian	*6	HO vs HE + WT	277	50–100	4.80	1.62–14.27
				HO + HE vs WT	233	50–100	2.40	1.28–4.49
				HO vs WT	58	50–100	2.16	0.28–16.96
				HE vs WT	182	50–100	2.09	0.66–6.62
			*28	HO vs HE + WT	101	50–100	1.27	0.20–7.94
				HO + HE vs WT	494	50–100	1.47	0.90–2.42
				HO vs WT	45	50–100	1.27	0.20–7.95
				HE vs WT	412	50–100	1.50	0.86–2.62
Zhang et al., 2017 [37]	1140	Asian	*6	HO + HE vs WT	n.r	60–225	2.03	1.54–2.68
					n.r.	<150	2.66	1.10–6.45
					n.r.	≥150	1.97	1.45–2.67
				HO vs WT	n.r.	60–225	2.95	1.83–4.75
					n.r.	<150	3.17	1.11–9.04
					n.r.	≥150	2.89	1.69–4.94
				HE vs WT	n.r.	60–225	1.83	1.36–2.46
					n.r.	<150	2.36	1.28–4.35
					n.r.	≥150	1.65	1.15–2.35
Yang et al., 2018 [38]	6742	Asian	*6	HO vs WT	1466	50–350	3.03	2.05–4.47
		Asian and Caucasian	*28	HE vs WT	1928	50–350	1.95	1.34–2.85
				HO vs WT	2609	50–350	3.50	2.23–5.50
				HE vs WT	3516	50–350	1.91	1.45–2.50

[a] RR instead of OR. CI = confidence interval, HE = heterozygous carrier, HO = homozygous carrier, n.r. = not reported, OR = odds ratio, RR = relative risk, vs = versus, WT = wild type.

Table 1b
Association between irinotecan-related severe diarrhoea and *UGT1A1* polymorphism.

Group[a]	n total	Ethnicity	Polymorphism	Association with irinotecan grade ≥ III diarrhoea				
				Comparison	n	Dose (mg/m^2)	OR	95% CI
Hu et al., 2010 [30]	1065	Asian and Caucasian	*28	HO vs HE + WT	1760	60–350	1.81	1.38–2.39
					355	≤125	1.06	0.57–1.99
					1405	>125	2.06	1.51–2.80
				HE vs WT	1265	60–350	1.73	1.25–2.40
					335	≤125	1.27	0.67–2.42
					930	>125	1.92	1.31–2.82
Liu et al., 2014 [28]	2015	Caucasian	*28	HO vs HE + WT	1980	80–350	1.71	1.18–2.47
					663	<150	1.41	0.82–2.43
					1317	≥150	2.04	1.23–3.38
				HO vs WT	1122	80–350	1.84	1.24–2.72
					348	<150	1.41	0.79–2.51
					774	≥150	2.37	1.39–4.04
				HE vs WT	1794	80–350	1.20	0.93–1.56
					593	<150	1.02	0.70–1.50
					1201	≥150	1.39	0.97–1.98
Cheng et al., 2014 [36]	1027	Asian	*6	HO vs WT	470	30–180	3.51	1.41–7.83
				HE vs WT	719	30–180	1.44	0.84–2.49
Chen et al., 2017 [34]	577	Asian	*6	HO vs HE + WT	307	50–100	6.25	1.51–25.0
				HO + HE vs WT	186	50–100	1.45	0.74–2.84
				HO vs WT	80	50–100	5.93	1.46–24.0
				HE vs WT	182	50–100	1.33	0.60–2.91
			*28	HO vs HE + WT	131	50–100	4.56	1.56–13.18
				HO + HE vs WT	447	50–100	4.90	2.02–11.88
				HO vs WT	104	50–100	17.64	2.58–120.66
				HE vs WT	439	50–100	4.36	1.74–10.91
Yang et al., 2018 [38]	6742	Asian	*6	HO vs WT	651	50–350	4.03	1.98–8.32
				HE vs WT	844	50–350	1.98	1.26–3.11
		Asian and Caucasian	*28	HO vs WT	1817	50–350	1.69	1.20–2.40
				HE vs WT	2521	50–350	1.45	1.07–1.97

[a] Hoskins et al. [26] did not find an association between irinotecan-related diarrhoea and homozygous carriers of *UGT1A1*28*; an OR was not reported. CI = confidence interval, HE = heterozygous carrier, HO = homozygous carrier, OR = odds ratio, RR = relative risk, vs = versus, WT = wild type.

replicate this increased risk [43]. For *UGT1A1*6*, one small study (n = 69) reported on an increased risk of febrile neutropenia in heterozygous carriers compared with wild-type patients [44].

The carriership of a *UGT1A1*28* allele also increased the risk of hospitalisation because of toxicity (level of evidence III and IV) [39,41]. No studies on this end-point have been reported for *UGT1A1*6*. The *UGT1A1*28* variant may also be associated with treatment-related mortality (level of evidence IV); treatment-related fatal neutropenia and bacteraemia occurred in 2 of 102 (2%) wild-type patients compared with 3 of 26 (11.5%) heterozygous or homozygous *UGT1A1*28* carriers ($p < 0.01$) [39]. No studies on *UGT1A1*6* reported on this end-point.

2] Clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*

The clinical validity and utility parameters were based on event rates reported in the meta-analysis by

Table 2
Clinical validity and utility of pre-therapeutic genotyping of *UGT1A1* in patients treated with irinotecan compared to the clinical validity and utility of *DPYD* in patients treated with fluoropyrimidines.

Parameter	*UGT1A1*6* [38]		*UGT1A1*28* [38]		*DPYD* variants [19]
	≥ grade III neutropenia	≥ grade III diarrhoea	≥ grade III neutropenia	≥ grade III diarrhoea	≥ grade III toxicity
Sensitivity	11%	11%	11%	13%	12–15%
Specificity	94%	94%	94%	92%	98%
PPV	33%	20%	30%	22%	20–24%
NPV	80%	89%	82%	85%	96–97%
NNG	376	564	79	127	210–251
NNT	8	11	9	14	5–6

NNG = number needed to genotype, NNT = number needed to treat, NPV = negative predictive value, PPV = positive predictive value.

Yang et al. [38]. We selected this meta-analysis because it included Asian as well as Caucasian patients with data on *UGT1A1*6* and *UGT1A1*28*, respectively; besides, it included the highest number of patients, and it was the most recent of all the identified meta-analyses [38].

The calculated sensitivity, specificity, and positive and negative predictive values for pre-therapeutic *UGT1A1* genotyping are provided in Table 2. The values proved to be comparable with the values of pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines [19]. These numbers indicate that pre-therapeutic *UGT1A1* genotyping would not identify all patients that experienced severe diarrhoea or neutropenia, but it would identify almost all the patients that had a good ability to tolerate irinotecan. This test may have false positive results, which may lead to a dose reduction of irinotecan, but this risk is unlikely to be relevant because only the starting dose of irinotecan will be reduced, followed by dose optimisation based on the tolerability of irinotecan in each individual patient. The low number of false negatives is of the highest importance because the expected severe toxicity of irinotecan in these patients can lead to hospitalisation and delay or even discontinuation of treatment, resulting in a reduced quality of life and treatment failure.

In addition, the NNT and NNG were calculated. For *UGT1A1*28,* the NNT (i.e. apply a dose reduction) to prevent ≥ grade III neutropenia was nine and to prevent ≥ grade III diarrhoea was 14. The NNG to prevent ≥ grade III neutropenia and ≥ grade III diarrhoea was 79 and 127, respectively. In view of these results, pre-therapeutic genotyping of *UGT1A1*28* seems even more clinically utile than pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines, which is mainly due to the higher prevalence of *UGT1A1*28*. For *UGT1A1*6,* the NNT to prevent ≥ grade III neutropenia was eight and the NNT to prevent ≥ grade III diarrhoea was 11, whereas the NNG was 376 and 564, respectively. *UGT1A1*6* seems less clinically utile than pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines because of the high NNG, which is caused by the low prevalence of this polymorphism. Only 2% of the East-Asian population is homozygous carriers of this polymorphism, and the polymorphism is not present in other populations. See Table 2 for a detailed overview.

3] Safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms

Several phase I *UGT1A1* genotype-guided dose-finding studies have been conducted. In these studies, the maximum tolerable dose (MTD) most often was lower than the standard dose of irinotecan in homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or in compound heterozygous carriers (*UGT1A1*6/*28*)

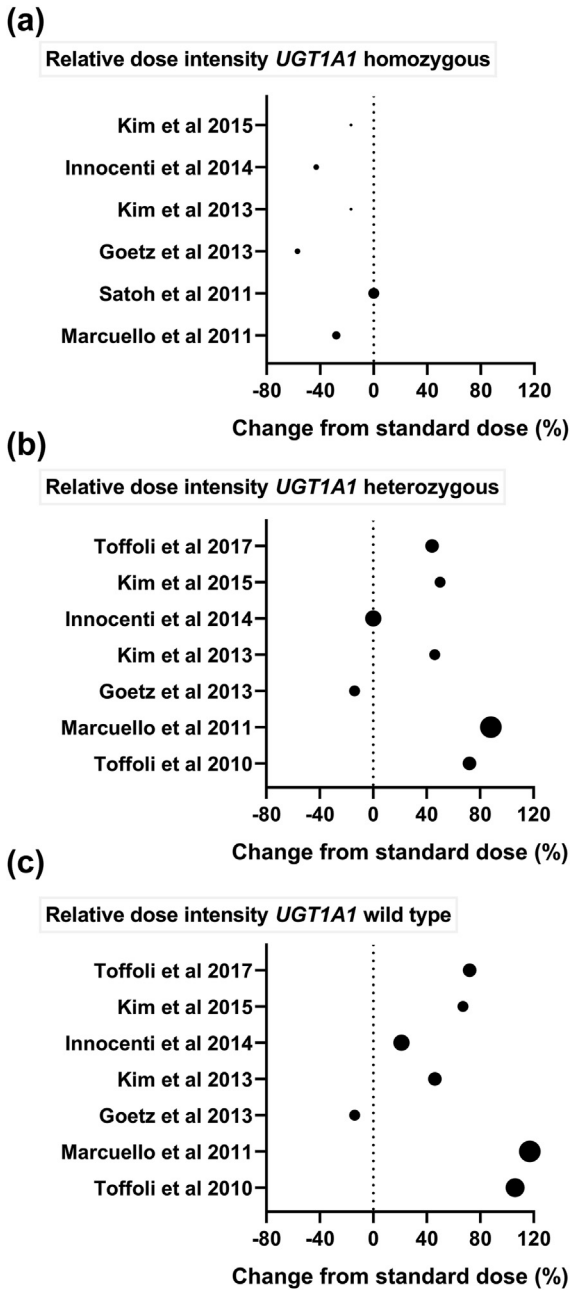

Fig. 1. The forest plot of outcomes of dose-finding studies of irinotecan per *UGT1A1* genotype category [22,45–51] Each dot represents the outcome of one study, presented as the difference between the maximum tolerable dose (MTD) reported and the standard dose of irinotecan in percentages. The size of each dot indicates the number of patients in each study in comparison to the other studies. Top: homozygous carriers of *UGT1A1*6* or *UGT1A1*28,* middle: heterozygous carriers of *UGT1A1*6* or *UGT1A1*28,* bottom: wild-type patients. For the exact numbers see Table 1 in the supplementary material.

(Fig. 1 + supplementary material table 1). Five [45–49] of six of these dose-finding studies found a lower MTD than the registered dose of irinotecan and, therefore, suggest to lower the irinotecan starting dose, with

Table 3
The overview of recommendations on drug labels and in guidelines for dosing of irinotecan in homozygous carriers of *UGT1A1* polymorphisms.

Organisation	Country/region	Dose reduction recommended for *UGT1A1* polymorphisms?	Dose recommendation	References
Drug labels		[a]*6 [a]*28		
FDA	USA	No Yes	≥1 dose level reduction	[55]
CBG-MEB	Netherlands	No No	Not applicable	[60]
PMDA	Japan	Yes Yes	No specification	[56]
HCSC	Canada	No Yes	No specification	[57]
Guidelines				
RNPGx-GPCO-unicancer	France	No[a] Yes	Dose 180–230 mg/m^2: 25–30% dose reduction Dose ≥ 240 mg/m^2: contra-indicated	[58]
KNMP-DPWG	Netherlands	Yes Yes	30% dose reduction	[59]

[a] The authors mention that this analysis is limited by the fact that other *UGT1A1* deficient variants are relevant in non-Caucasian populations, particularly the *6 and *27 alleles in Asian populations. FDA = Food and Drug Administration, CBG-MEB = Dutch Medicines Evaluation Board, PMDA = Pharmaceuticals and Medical Devices Agency, HCSC= Health Canada/Santé Canada, RNPGx = National Pharmacogenetics Network, GPCO = Group of Clinical Onco-pharmacology, KNMP = Royal Dutch Association for the Advancement of Pharmacy, DPWG = Dutch Pharmacogenetics Working Group.

relative dose intensities ranging from 42 to 83% [22,45–49]. Moreover, the single study that reported a 100% relative dose intensity stated that homozygous carriers may receive irinotecan at a starting dose of 150 mg/m^2, but in subsequent cycles dose reductions or treatment delays were indicated in 12 of 16 patients (75%) [22].

In heterozygous carriers of *UGT1A1*6* or *UGT1A1*28* and wild-type patients, the MTD was often higher than the standard dose. Five [45,47,49–51] of seven and six [45,47–51] of seven dose-finding studies found a higher MTD than the standard dose in heterozygous carriers and wild-type patients, with relative dose intensities ranging from 86 to 188% and 86–217%, respectively [45–51]. Most of the patients in these dose-finding studies had a relatively low ECOG performance score (ranging from 0 to 1) compared with the real-world population, which might have led to overestimation of the MTD.

Three prospective genotype-guided dosing studies tested the reduced starting dose of irinotecan for homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or *UGT1A1*6/*28* [11,52,53], and their findings are in line with the dose-finding studies presented in Fig. 1. Fuji et al. [11] reduced the starting dose of irinotecan from 150 mg/m^2 to 120 mg/m^2 (relative dose intensity 80%) in the homozygous group (n = 10), finding no significant differences in adverse events or tumour response compared with the heterozygous carriers and wild-type patients (n = 43) in this study. Xu et al. [53] conducted a preplanned analysis in the AXEPT trial (XELIRI or FOLFIRI schedule, n = 650). Fifty homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or *UGT1A1*6/*28* were enrolled; the starting dose of irinotecan was reduced to 150 mg/m^2 and was well tolerated [53]. Boisdron-Celle et al. [52] conducted a proof-of-concept trial in which patients intended to be treated with FOLFIRI-cetuximab were stratified by their *UGT1A1*28* genotype and received irinotecan dose intensification provided that treatment was well-tolerated. Eighty-five patients were enrolled, and mean irinotecan doses at 3 months were 247, 210, and 140 mg/m^2 for wild-type, heterozygous and homozygous carriers, respectively (relative dose intensities: 137%, 116% and 78%, respectively) [52].

Currently, there is one randomised controlled trial in which 82 wild-type patients and heterozygous carriers of *UGT1A1*28* were randomised to receive either high-dose FOLFIRI or standard FOLFIRI [54]. In the high-dose FOLFIRI group, the irinotecan dose was 300 mg/m^2 for wild-type patients and 260 mg/m^2 for heterozygous patients. In the control group, the dose was 180 mg/m^2, irrespective of the genotype. The authors concluded that *UGT1A1* wild-type patients and heterozygous carriers of *UGT1A1*28* may receive higher doses of irinotecan and showed a higher objective response

rate than those receiving the standard dose (67.5 versus 43.6%; OR = 1.73 [95% CI:1.03–2.93, p = 0.001]), without a significantly increased risk for severe toxicity (22.5% versus 20.5%).

4] Availability of dose recommendations for irinotecan in carriers of UGT1A1 polymorphisms

Various dose recommendations for irinotecan in homozygous carriers of *UGT1A1*28* were found on drug labels and in guidelines (Table 3). Most of the national medicines authorities and guideline working groups recommend to apply a dose reduction of 25–30% in homozygous carriers of *UGT1A1*28* [55–59]. Only the Dutch national medicines authority does not recommend dose reduction in homozygous carriers of *UGT1A1*28* treated with conventional irinotecan [60].

For homozygous carriers of *UGT1A1*6*, less information was found on drug labels and in guidelines, which might be because of the fact that this polymorphism only occurs in the Asian population. However, the Japanese drug label states that patients should be selected for treatment based on their stage, general condition and the *UGT1A1* genotype, although no specific dose recommendations are provided [56].

Only the French working group mentions dose recommendations for *UGT1A1*28* heterozygous and wild-type patients, stating that the administration of an intensified dose of irinotecan (240 mg/m^2) is only possible in wild-type patients. In heterozygous patients, dose intensification may be applied in the absence of additional risk factors and under strict medical surveillance [58]. Obviously, this is an off-label dose recommendation.

Moreover, the Clinical Pharmacogenetics Implementation Consortium assigned level A to this gene–drug interaction, indicating that genetic information should be used to change the prescription of this drug [61].

5] Evidence of cost benefits of pre-therapeutic genotyping of *UGT1A1*

Besides improved patient safety, pre-therapeutic genotyping of *UGT1A1* is also likely to be cost-effective or even cost-saving. To date, four studies [62–65] assessed the cost effectiveness of pre-therapeutic genotyping followed by a 20%–25% dose reduction of irinotecan in homozygous variant carriers of *UGT1A1*28* in Caucasian populations, or in carriers of both *UGT1A1*6* and *UGT1A1*6/*28* in a Chinese population, compared with no genotyping. This was assessed with decision-analytic models using clinical and genetic data from the literature. All studies concluded that pre-therapeutic genotyping was a cost-saving strategy compared with no genotyping, reporting cost reductions due to pre-therapeutic genotyping ranging from 112 euro up to 596 euro per patient.

Roncato et al. [66] conducted the first retrospective clinical validation study in an Italian hospital setting. They assessed the association between the *UGT1A1*28* genotype and the cost of toxicity management. The mean costs per patient were 812€ for wild-type patients, 1119€ for heterozygous variant carriers, and 4886€ for homozygous variant carriers, which illustrates that the costs of irinotecan-related toxicity are significantly higher in patients carrying a homozygous or heterozygous variant of *UGT1A1*28* than in wild-type patients. The cost driver was hospitalisation, which accounted for 82% of all toxicity costs. Six of 22 (27%) homozygous variant carriers were hospitalised for irinotecan-related toxicity, compared with 10 of 122 (8.2%) heterozygous variant carriers and 6 of 109 (5.5%) wild-type patients.

4. Discussion

Based on the available literature, we conclude that pre-therapeutic genotyping of *UGT1A1* in patients initiating treatment with irinotecan improves patient safety and is likely to be cost-saving. In this review, the available evidence for pre-therapeutic genotyping of *UGT1A1*6* and *UGT1A1*28* in patients treated with irinotecan was assessed in a structured and objective manner, and data were assessed based on five main criteria.

Level of evidence I exists for the association of *UGT1A1*28* and *UGT1A1*6* and irinotecan-induced severe neutropenia or severe diarrhoea; level III for the association between *UGT1A1*28* and febrile neutropenia, and level III and IV for treatment-related hospitalisation and mortality, respectively. In addition, the clinical validity and utility of pre-therapeutic genotyping of *UGT1A1* proved to be acceptable and comparable with the clinical validity and utility of pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines. Because this *DPYD* test has recently been recommended by the European Medicines Agency [18], pre-therapeutic *UGT1A1* genotyping might also be considered clinically valid and utile.

Moreover, the combined conclusion of multiple dose-finding studies indicates that the current standard way of dosing of irinotecan is not safe for homozygous carriers of *UGT1A1*6* or *UGT1A1*28*, whereas wild-type patients might even tolerate higher doses of irinotecan. A complementing finding is that the evidence described before has been taken up in various drug labels and guidelines providing specific dose recommendations for irinotecan in homozygous carriers of *UGT1A1*28* or *UGT1A1*6*: most of the national

medicines authorities and guideline working groups recommend to apply an initial dose reduction of 25–30% in these patients.

Finally, pre-therapeutic genotyping of *UGT1A1* is likely to be cost-saving. Homozygous carriers of *UGT1A1*28* or *UGT1A1*6* were shown to have ~six-fold higher irinotecan-related toxicity costs than wild-type patients, mainly due to costs for hospitalisation for toxicity treatment. In comparison, patients carrying a *DPYD* variant seem to have ~four-fold higher toxicity costs than wild-type patients [67]. This indicates that the costs of pre-therapeutic genotyping seem to be outweighed by the savings achieved by preventing the costs of toxicity treatment.

A limitation on the available evidence for *UGT1A1* genotype–guided dosing of irinotecan is the absence of a randomised controlled trial on treatment outcome, i.e. overall survival. However, such a trial is hardly feasible and is not likely to be conducted because at least a roughly estimated 300 homozygous individuals per arm would be needed for sufficient power, requiring a total of at least 6000 patients to be prospectively screened for inclusion. Moreover, with the available evidence favouring pre-therapeutic genotyping, it seems not ethical to randomise patients and patients may not be willing to participate in such a trial. Nonetheless, it is unlikely that genotype-guided dosing for homozygous carriers of *UGT1A1*28* or *UGT1A1*6* will negatively affect overall survival because the recommended dose reduction leads to equal systemic exposure to SN38 in these patients as in wild-type patients treated with standard-dose therapy [46,68]. Moreover, the addition of other *UGT1A1* variants such as *UGT1A1*93* [4] and variants of other genes encoding for other enzymes such as *UGT1A7* and *UGT1A9* [69] might improve the predictive ability of *UGT1A1* genotype-guided dosing of irinotecan. Of interest, a prospective *UGT1A1*93* genotype-guided dose-finding trial is currently ongoing (https://www.trialregister.nl/- trial NL6270 [NTR6612]).

Overall, based on this evaluation, all five criteria that were assessed showed that the available evidence is in favour of pre-therapeutic genotyping of *UGT1A1*. We recommend that all patients starting with irinotecan chemotherapy should be genotyped for *UGT1A1*28*; for Asian patients, the *UGT1A1*6* polymorphism should also be tested. If a patient is homozygous for *UGT1A1*28* or *UGT1A1*6*, a dose reduction of 25–30% should be performed for all dosing regimens of irinotecan. Patients that are compound heterozygous *UGT1A1*6/*28* are considered poor metabolisers. Although less evidence is available, the available studies and the Japanese drug label suggest to treat these patients conform homozygous carriers of *UGT1A1*6* [11,22,35,56,65]. Dose-escalation in wild-type patients is potentially safe, but there is not enough literature on clinical outcomes, and hence further research is warranted. Because of the presence of a wide interpatient variability in the pharmacokinetic parameters of irinotecan, a step-up–based approach based on therapeutic drug monitoring might be of interest [70]. In addition, although turn-around time and costs of *UGT1A1* genotyping may be a challenging issue, integration of *UGT1A1* genotyping into tumour sequencing programs may potentially enable genome testing without additional genotyping costs [71].

In summary, we conclude that pre-therapeutic genotyping of *UGT1A1* followed by genotype-guided dosing in patients treated with irinotecan is to be favoured over standard treatment and should therefore become standard of care and be implemented in oncology guidelines, such as the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.

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Conflict of interest statement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.09.007.

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