Precision medicine using pharmacogenomic panel testing

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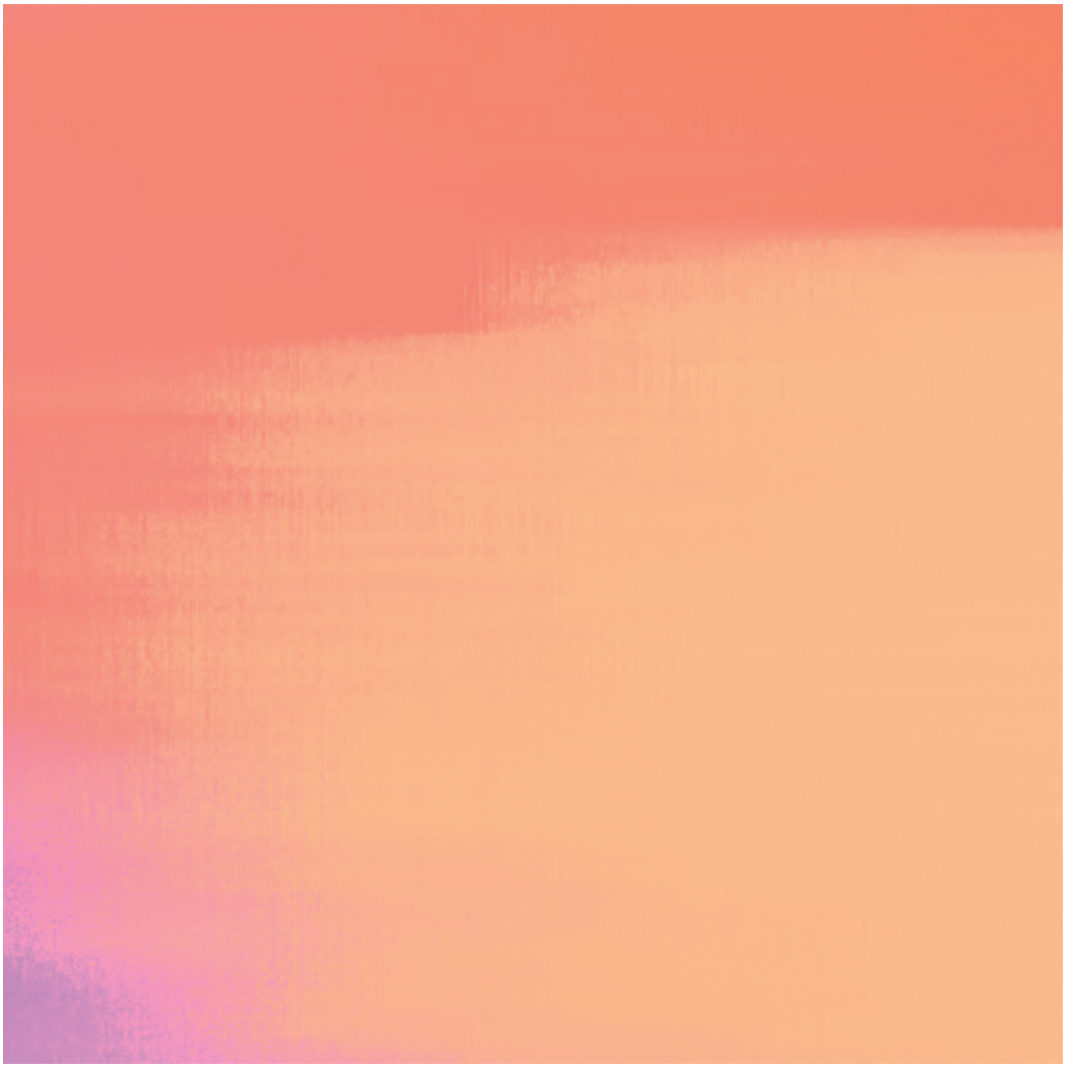

PART IV

Quantifying the Impact on Patient Outcomes and Cost-Effectiveness

Chapter 9:

Cost-Effectiveness of Pharmacogenomics-Guided Prescribing to Prevent Gene-Drug-Related Deaths: A Decision-Analytic Model

Submitted

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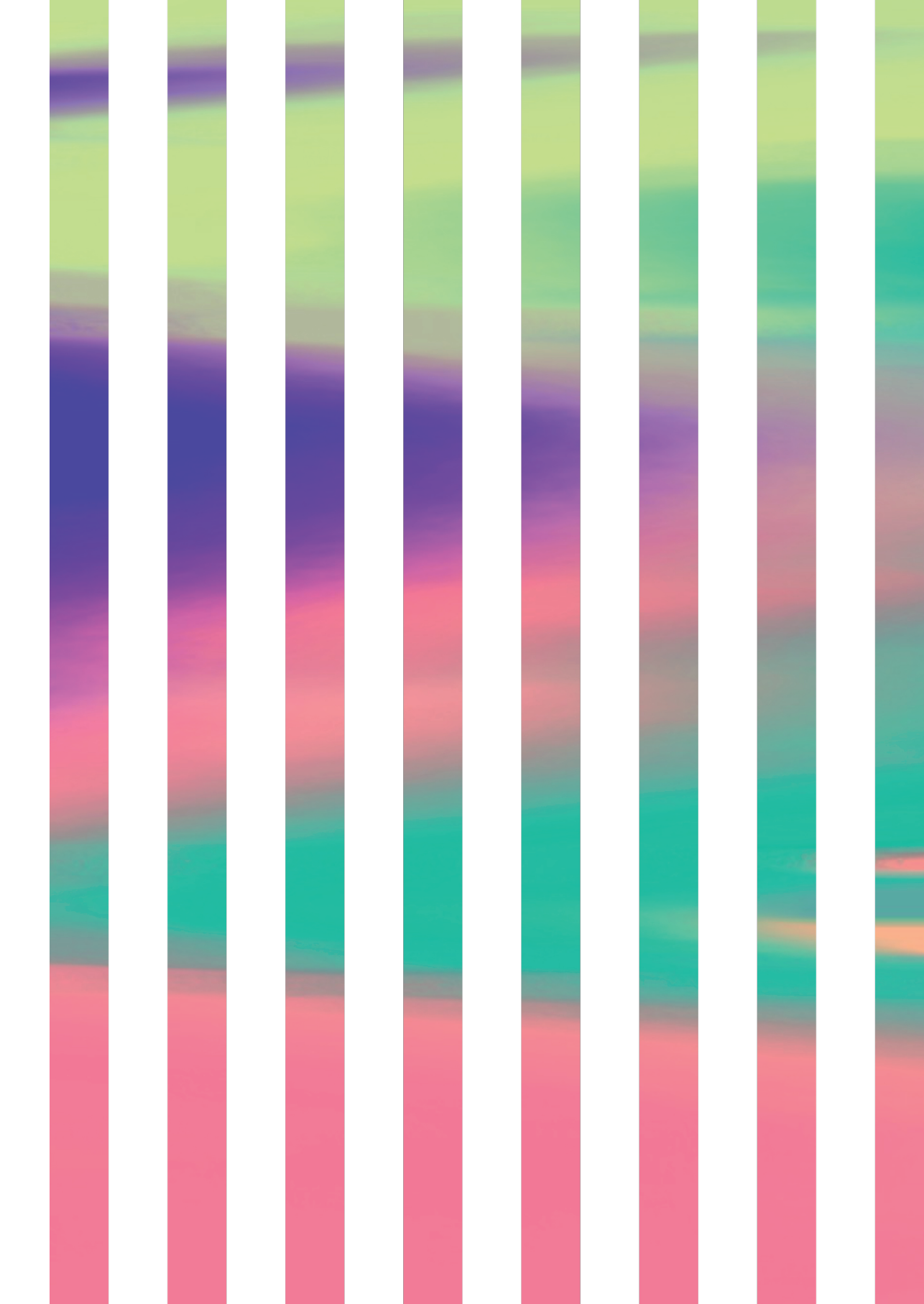

ABSTRACT

Background: Prospective studies support the clinical impact of pharmacogenomics (PGx)-guided prescribing. A sub-set of these drug-gene interactions (DGIs) has been categorized as "essential" by the Dutch Pharmacogenetics Working Group (DPWG). However, the collective clinical impact and cost-effectiveness of this sub-set is yet undetermined.

Objective: To assess the clinical impact and cost-effectiveness of "essential" PGx tests to prevent gene-drug-related deaths when adopted nation-wide.

Design: Decision-analytic model.

Data sources: Absolute risks of gene-drug-related death for tested and untested predicted phenotype categories were systematically extracted from publications underlying the DPWG recommendations; predicted phenotype frequencies were extracted from a Dutch sample (n=1,023); the number of patients initiating individual drugs of interest was extracted from the nation-wide prescription database; and the cost of PGx-testing, clinician interpretation time, and drugs were based on national standardized prices.

Target population: Patients in the Netherlands initiating clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine or irinotecan treatment.

Time Horizon: One year.

Perspective: Healthcare sector.

Intervention: A single-gene PGx-test for *CYP2C19, DPYD, TPMT or UGT1A1* to guide prescribing based on the DPWG recommendations.

Outcome measures: Number and cost per gene-drug-related death prevented.

Results: For 148,128 patients initiating one of seven drugs in a given year, costs for PGx-testing, interpretation, and drugs would increase by €21.4 million. Of these drug initiators, 35,762 (24.1%) would require an alternative dose or drug. PGx-guided prescribing would relatively reduce gene-drug-related mortality by 10.6% (range per DGI: 8.1% – 14.5%) and prevent 419 (0.3% of initiators) deaths a year. Cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death (range per DGI: €-752,000 – €633,000).

Limitations: Risks of gene-drug-related death were extracted from studies powered on intermediate outcomes.

Conclusion: Adoption of PGx-guided prescribing for "essential" DGIs potentially saves the lives of 0.3% of drug initiators, at reasonable costs.

INTRODUCTION

Pharmacogenomics(PGx)-guided prescribing promises to personalize drug therapy by using an individual's germline genetic makeup to guide dose and drug selection (1, 2). This ameliorates the conventional 'trial and error' approach of drug prescribing, thereby reducing risk of lack of efficacy and adverse drug events (ADRs) (3). ADRs are a significant burden for individual patients and society and are an important cause of emergency department visits and hospital admissions (4-6). The resulting economic burden in the United States has been estimated at $30 billion to $136 billion annually (7). Several prospective studies support the clinical impact of individual gene-drug interactions (DGIs) to either optimize dosing (8-12) or drug selection (13, 14). Additionally, both the Clinical Pharmacogenetics Implementation Consortium (CPIC) (15, 16) and the Dutch Pharmacogenetics Working Group (DPWG) (17-19) have developed guidelines on incorporating PGx results into drug prescribing. Nevertheless, ambiguity remains regarding whether and which PGx tests should be prioritized for implementation into routine care (20). In an effort to overcome this inconclusiveness and to direct clinicians on requesting relevant PGx tests, the DPWG developed the Clinical Implication Score, where DGIs classified as "essential" direct clinicians to request a single-gene PGx test pre-therapeutically to guide dose and drug selection of the interacting drug (19). The Clinical Implication Score is based on the severity of clinical consequences associated with the DGI, the level of evidence for the association, the number needed to genotype to prevent an ADR with Common Terminology Criteria of Adverse Events (CTCAE) grade ≥ 3, and the level of PGx information included in the drug label. "Essential" DGIs comprise of high-risk drugs and corresponding recommendations intend to prevent severe clinical consequences such as gene-drug-related death. Therefore, they may be considered a minimum list of DGIs for which pre-therapeutic PGx-testing should be performed.

While numerous implementation barriers have been overcome, pre-therapeutic PGx-testing for all "essential" DGIs is not yet routine care and significant barriers preventing adoption remain (21-23). A prominent barrier is the lack of reimbursement of single-gene PGx tests, despite the availability of numerous cost-effectiveness analyses (24, 25). Reimbursement of PGx tests for "essential" DGIs may be supported by studies quantifying the impact and cost-effectiveness of wide-spread adoption. Here, impact on the most severe outcome, mortality, may be most impactful.

Although the incidence of DGIs, when adopted nation-wide, has been estimated (26-28) and the cost-effectiveness of numerous DGIs in single-gene scenarios have been determined (24, 25), the collective downstream effect of "essential" DGIs on clinical outcomes and cost-effectiveness after wide-spread adoption remains undetermined. Therefore, we aim to assess the collective impact and cost-effectiveness of PGx for DGIs categorized as "essential" to prevent gene-drug-related deaths when adopted nation-wide in The Netherlands using a decision-analytic model.

METHODS

Study Design

We developed a decision-analytic model to assess the number and cost of gene-drug-related deaths prevented with PGx-guided initial dose and drug selection for "essential" DGIs, among patients initiating potentially interacting drugs in the Netherlands when compared to standard of care in one year. DGIs were selected based on the following criteria: 1) the clinical implication score is "essential", meaning that DPWG advises pre-therapeutic genotyping and 2) the DGI has clinical relevance score F (CTCAE Grade 5) and is therefore associated with gene-drug-related death for at least one predicted phenotype category. These selection criteria yielded the interactions between four genes (*CYP2C19*, *DPYD*, *TPMT*, and *UGT1A1)* and seven drugs (clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine, and irinotecan). See **Table 1** for an overview of selected gene-drug pairs. When the DPWG recommendations suggested either dose reduction or an alternative drug, this model assumed dose reduction as the intervention.

Decision Analytic Model

The following model was used to calculate the number of gene-drug-related deaths prevented within one year:

$$N_{GDRDP} = \sum_{Drug=1}^{7} N_{Drug} \times \sum_{Pheno} P_{Pheno} \times \left(AR^{SoC}_{Drug,Pheno} - AR^{PGx}_{Drug,Pheno}\right)$$

N_{GDRDP}=Number of gene-drug-related deaths prevented; N_{Drug}=Number of drug initiators; P_{Pheno}=predicted phenotype category frequency; pheno=predicted phenotype category; AR=absolute risk of gene-drug-related death within one year; SoC=standard of care; PGx=pharmacogenomics guided initial drug and dose selection;

The following model was used to calculate the cost of gene-drug-related deaths prevented within one year:

$$Cost = \sum_{Drug=1}^{7} N_{Drug} \times \sum_{Pheno} P_{Pheno} \times \left(Cost_{PGx} + Cost_{HCP} + Cost^{PGx}_{Drug,Pheno} - Cost^{SoC}_{Drug,Pheno}\right)$$

Cost=extra costs ; N_{Drug}=Number of drug initiators; PGx=single-gene test; HCP = physician and pharmacist time for interpretation and discussion of actionable PGx results; C_{Drug}=Medication costs; SoC=standard of care; PGx=pharmacogenomics guided initial drug and dose selection

Finally, the cost per gene-drug-related death prevented was calculated by dividing cost by the number of deaths prevented both per individual DGI and overall.

Model Inputs

Number of Patients Initiating One of the Seven Drugs in The Netherlands

The number of patients a year initiating each of the seven drugs was estimated by multiplying the yearly number of users by the ratio of initiators and users. The yearly number of users was extracted from the Dutch nation-wide GIP databank from the most recent available year; azathioprine, clopidogrel, systemic fluorouracil and irinotecan from 2018, mercaptopurine and tioguanine from 2017 and capecitabine from 2014 (29). For fluorouracil only aggregated systemic and cutaneous data are reported in the GIP databank. To exclude the cutaneous users, we multiplied total number of users with the percentage of systemic fluorouracil users in the Leiden University Medical Center (LUMC) in 2018. The ratio of initiators and users was extracted per drug from the Leiden University Medical Center (LUMC) electronic medical record (EMR) for 2013 until 2018. Here users were defined as those who had a prescription for that drug in their EMR in this period and initiators were defined as users who lacked a prescription for that drug before 2018. See **Appendix 1** for an overview of the used ratios and calculated number of nation-wide drug initiators.

Predicted Phenotype Category Frequencies

The predicted phenotype frequencies for the selected genes were derived from a Dutch sample (n=1,023) (30). The variants tested to determine phenotype have been described in detail (31). The genotypes are translated into predicted phenotype categories based on functionalities as described in the DPWG recommendations (17, 18).

Risk of Gene-Drug-Related Death

The most severe outcome among patients receiving standard of care, as reported in literature underlying the DPWG recommendations, associated with each "essential" DGI is shown in Table 1. Each DPWG recommendation suggests either a dose adjustment or selection of an alternative drug, to reduce the risk of both gene-drug-related deaths and other less severe ADRs. For our model, we extracted the absolute risk of gene-drug-related death within one year both in patients receiving the PGx-informed and standard of care (i.e. PGx uninformed) drug treatments for each predicted phenotype category independently, since the risk of gene-drug-related death varies across predicted phenotype categories. For example, the risk of fluoropyrimidine-induced toxicity increases with decreasing *DPYD* gene activity scores (GAS). Furthermore, when a PGx test is used to guide dose selection, individuals with an actionable phenotype (*DPYD* GAS 0-1.5) have a reduced risk of fluoropyrimidine-induced toxicity compared to individuals with an actionable phenotype using a normal dose. On the other hand, the risk of fluoropyrimidine-induced toxicity in individuals with a non-actionable predicted phenotype (*DPYD* GAS 2) will have the same mortality risk, regardless of being tested, since the dose is the same in both groups. Therefore, we have extracted the absolute risk of gene-drug-related death for each predicted

phenotype category from the literature, across three groups: 1) tested-actionables (e.g. DPYD GAS 0, 0.5, 1 and 1.5 with PGx informed reduced dose), 2) non-actionables (e.g. DPYD GAS 2 with normal dose) and 3) untested-actionables (e.g. DPYD GAS 0, 0.5, 1 and 1.5 with normal dose). The actionable drug-gene pairs are categorized in **Table 1**.

A systematic methodology was used to select relevant publications from publications underlying the DPWG guideline which were suitable for risk extraction and is described in detail in **Appendix 2**. In brief, six steps are performed chronologically until relevant publications have been selected from which absolute risk of gene-drug-related death for each of the tested and untested predicted phenotype categories can be extracted. The scientific rigor of publications decreases with each step and corresponds to the DPWG quality of evidence score (17, 18). The first two steps select publications powered on mortality, the second two steps select publications powered on intermediate outcomes that are associated with mortality and the last two steps resort to additional literature search or estimation. Risk extraction is performed by using methodology corresponding to that step. Each extracted absolute risk of gene-drug-related death is given a certainty score based on the step in which publications are selected. The certainty score ranges from 4 (very certain) to 0 (very uncertain). An overall certainty score per DGI is calculated by taking the mean of the certainty scores of all tested and untested predicted phenotype categories. The systematic selection of publications and extracted absolute risks of gene-drug-related related deaths are described in **Appendix 3.**

Costs

Costs are estimated from a health care perspective, with a one-year time-horizon, and are reported in Euros. The costs of different single-gene PGx tests were based on single-gene prices set in the LUMC in 2018 and on prices from the Dutch Healthcare Authority (NZa). This includes sample collection, analysis, and report of the predicted phenotype and dosing recommendation to the requesting pharmacist. The pharmacist time to record and discuss results with the physician and patient was set at 18 minutes. The physician time to discuss results with the pharmacist was set at 6 minutes. Time spent was multiplied by the hourly salaries of Clinical Pharmacists and Medical Specialists as standardized in Dutch Academic Hospitals in 2019 (32). The cost of drugs for both standard of care and PGx-guided treatments was calculated for a time-horizon of one year. The applied dose was based on the most common indication for the relevant drug and calculated using a base case of 75kg and a body surface area of 1.7m^2. The price of drugs was extracted from the national drug price registry (33) by selecting the least expensive suitable dose and formulation. See **Appendix 4** for an overview of the costs used in the model.

Table 1 Selected "essential" gene-drug pairs, their potential consequences and DPWG recommendation per phenotype category

Drug	Gene	Predicted Phenotype	Actionable DGI	DPWG recommendation	Most severe consequence*
Azathioprine	*TPMT*	*TPMT* EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe myelosuppression
Capecitabine	*DPYD*	*DPYD* GAS 0	Yes	Alternative drug	Fluoropyrimidine induced toxicity
		DPYD GAS 0.5/PHENO	Yes	Dose adjustment based on DPD phenotype	Fluoropyrimidine induced toxicity
		DPYD GAS 1.0	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 1.5	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 2.0	No	-	-
Clopidogrel	*CYP2C19*	*CYP2C19* EM	No	-	-
		CYP2C19 IM	Yes	Dose increase to 200% or alternative drug	
		CYP2C19 PM	Yes	Alternative drug (ticagrelor, prasugrel or dipyridamole)	Cardiovascular death
		CYP2C19 UM	No	-	Cardiovascular death
Fluorouracil (systemic)	*DPYD*	*DPYD* GAS 0	Yes	Alternative drug	Fluoropyrimidine induced toxicity
		DPYD GAS 0.5/PHENO	Yes	Dose adjustment based on DPD phenotype	Fluoropyrimidine induced toxicity
		DPYD GAS 1.0	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 1.5	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 2.0	No	-	-
Irinotecan	*UGT1A1*	*UGT1A1* *1/*1	No	-	-
		UGT1A1 *1/*28	Yes	-	-
		UGT1A1 *28/*28	Yes	Dose reduction to 70%	Severe myelosuppression and diarrhea
		UGT1A1 IM	No	-	-
		UGT1A1 PM	No	Dose reduction to 6%	Severe myelosuppression and diarrhea
Mercaptopurine	*TPMT*	*TPMT* EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe myelosuppression
Tioguanine	*TPMT*	*TPMT* EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe pancytopenia

*Clinical relevance score: CTCAE 5 (death), as reported in the summary of literature underlying the DPWG recommendations

Model Assumptions

The adoption of PGx test requesting among initiators was assumed 100%, DPWG recommendation adherence was assumed 100% and the dose of drugs to be as per protocol for the indications which were investigated in publications from which risk data was extracted. Regarding the target population and allele frequencies, the ethnicity was assumed Caucasian, and patients were assumed to use similar comedications as patients enrolled in studies from which risks were extracted.

Role of the Funding Source

This study was funded by the European Community's Horizon 2020 Program under grant agreement No.668353 (U-PGx). The funder played no role in this study's design, conduct or report.

RESULTS

As shown in **Table 2**, on a population of 17 million Dutch inhabitants, 148,128 patients initiate one of seven drugs in a given year, of which the clopidogrel initiators form the largest group (79.6%).

Impact on Costs

The total costs of single-gene PGx-testing, interpretation, and additional drugs would be €21.4 million (mean €145 per patient), of which the relevant single-gene test comprises 90.7% (€19.4 million in total, mean €131 per patient). Of these drug initiators, 35,762 (24.1%) would have an actionable DGI, requiring an alternative dose or drug. Health care professional (HCP) discussion of these actionable results would cost €686,000 (€16 per actionable patient). The extra drug costs made for initiating PGx-guided drug treatment is €1.5 million (€10 per patient), of which €2.4 million additional costs as a result of alternative drug treatment and €941,000 costs saved as a result of dose lowering. Interestingly, PGx-guided drug treatment costs are cost-saving for most DGIs (range per cost-saving DGI: 0.7%-4.6%), except the clopidogrel-*CYP2C19* interaction where the drug costs are €2.8 million higher (€24 per patient, +162%) than standard of care. For the irinotecan-*UGT1A1* interaction, the costs of drugs saved in the PGx-guided group surmounts the cost of PGx-testing and HCP interpretation combined, making the intervention cost-saving with €481,000 on irinotecan drug costs.

Number of Gene-Drug-Related Deaths Prevented

As shown in **Table 3**, PGx-guided initial dose and drug selection would relatively reduce total gene-drug-related mortality by 10.6% (range per DGI: 8.1% – 14.5%) and prevent 419 (0.3% of initiators) deaths per year. The average certainty score was 2.5 (fairly

certain) when weighed for deaths prevented or for number of patients and ranged from of 0 (very uncertain) to 3 (certain) for individual DGIs.

Cost-Effectiveness Analysis

Preventing 419 gene-drug-related deaths with an increase of €21.4 million in healthcare costs, cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death (range per DGI: €-752,000 – €633,000). For the irinotecan-*UGT1A1* interaction, PGx-guided treatment reduces both mortality and costs (resulting in a negative cost-effectiveness ratio).

DISCUSSION

Nation-wide adoption of PGx-guided initial dose and drug selection of "essential" DGIs can potentially save the lives of 419 (0.3% of drug initiators) a year at a cost of €55,000 per prevented death. The weighted average certainty score for this analysis 2.5 (fairly certain). In high-income countries an intervention is considered cost-effective when one gained quality-adjusted life year (QALY) costs less than a threshold between €20,000-60,000 (34). Since PGx-guided pharmacotherapy prevents gene-drug related deaths, it will contribute numerous QALYs; the magnitude of which is associated with the number of additional years that is gained by preventing the fatal gene-drug associated ADR. The investigated seven drugs are generally used to treat life-threatening diseases, and as a result, if treatment is effective and safe, patients will have a below-average though still considerable life-expectancy. Therefore, the additional cost of €51,000 per prevented death is well under the cost-effectiveness thresholds and can be considered reasonable and cost-effective.

Comparison to Current Literature

To our knowledge, we are the first to quantify both the collective impact and cost-effectiveness of nation-wide PGx-guided initial drug and dose selection for DGIs categorized as "essential" on mortality outcomes. Regarding collective impact, previous efforts have quantified the incidence of DGIs when adopted nation-wide (26-28). Bank *et al*. estimated that nation-wide adoption in the Netherlands of all DPWG recommendations would result in 23.6% of new prescriptions for PGx drugs would have an actionable DGI requiring adjustment of pharmacotherapy (27). However, the downstream impact on clinical outcomes were undetermined. In terms of cost-effectiveness, previous efforts have assessed individual drug-gene interactions but have not assessed the collective cost-effectiveness of "essential" DGIs. These include investigation of *HLA-B**57:01 testing before abacavir initiation (35), *HLA-B**58:01 testing before allopurinol initiation (36), *HLA-B**15:02 and *HLA-A**31:01 before carbamazepine initiation and *CYP2C9* and *VKORC1* guided initial dosing of warfarin (37).

Table 2 Overall costs of PGx-testing, pharmacist and physician time for interpretation and drug treatment

Drug	N drug initiators	Cost of PGx test/€ per initiator	Average cost of HCP interpretation of actionable PGx result/€ per initiator*	Average cost of drugs for standard of care (SoC) treatment /€ per initiator in one year	Average cost of drugs for PGx-guided treatment/€ per initiator in one year	Difference in average drug costs (SoC-PGx)‡ (% saved) /€ per initiator in one year	Total costs for all initiators†/€
Azathioprine	6,979	132	1	248	237	11 (4.6%)	**854,659**
Capecitabine	8,860	132	1	1,204	1,158	46 (3.9%)	**775,246**
Clopidogrel	117,900	132	5	15	38	-24 (-62%)	**18,923,430**
Fluorouracil (systemic)	6,765	132	1	82	79	3 (4.0%)	**880,112**
Irinotecan	2,593	66	2	14,842	14,588	253 (1.7%)	**-481,019**
Mercaptopurine	2,177	132	1	1,956	1,875	81 (4.3%)	**114,172**
Tioguanine	2,854	132	1	1,088	1,080	7 (0.7%)	**359,471**
TOTAL for all initiators/€	**148,128**	**19,381,790**	**586,167**	**60,519,056**	**61,977,169**	**-1,458,113**	**21,426,070**
MEAN per initiator/€	**-**	**131**	**16***	**409**	**418**	**10**	**145**

PGx = pharmacogenomic; HCP = health care professional; *note: only those with an actionable drug-gene interaction will be interpreted by an HCP; †$[cost_{PGxtest}]+[cost_{pharmacist\ and\ physician\ time}]-[cost_{drugs}]$.

Table 3 Cost-effectiveness of PGx-guided pharmacotherapy for gene-drug interactions to prevent gene-drug-related deaths

Drug	N drug initiators	Predicted Phenotype	Phenotype frequency	N actionable DGI*	Absolute risk reduction/% †	N gene-drug-related deaths with standard of care	N gene-drug-related deaths with PGx-guided care	N gene-drug-related deaths prevented§ (RRR%)	Number Needed to Genotype (NNG)‡	Certainty score	Cost to prevent 1 GDR death‖/€
Azathioprine	6,979	*TPMT* EM	0.912	0	0.0000	15.8	13.5	**2.3 (14.5%)**	3,057	2 (fairly certain)	**374,411**
		TPMT IM	0.087	607	0.0036						
		TPMT PM	0.001	7	0.0097						
Capecitabine	8,860	*DPYD* GAS 0	0.001	9	0.0076	22.4	20.6	**1.8 (8.1%)**	4,863	1 (uncertain)	**425,488**
		GAS 0.5/PHENO	0.000	0	0.0058						
		DPYD GAS 1.0	0.018	157	0.0039						
		DPYD GAS 1.5	0.054	481	0.0024						
		DPYD GAS 2.0	0.925	0	0.0000						
Clopidogrel	117,900	*CYP2C19* EM	0.673	0	0.0000	3,887.8	3,477.0	**410.8 (10.6%)**	287	3 (certain)	**46,064**
		CYP2C19 IM	0.245	28,893	0.0030						
		CYP2C19 PM	0.037	4,407	0.0005						
		CYP2C19 UM	0.045	0	0.0000						
Fluorouracil	6,765	*DPYD* GAS 0	0.001	7	0.0076	17.1	15.7	**1.4 (8.1%)**	4,863	1 (uncertain)	**632,612**
		GAS 0.5/PHENO	0.000	0	0.0058						
		DPYD GAS 1.0	0.018	120	0.0039						
		DPYD GAS 1.5	0.054	367	0.0024						
		DPYD GAS 2.0	0.925	0	0.0000						
Irinotecan	2,593	*UGT1A1* *1/*1	0.430	0	0.0000	4.7	4.1	**0.6 (13.6%)**	4,055	2 (uncertain)	**-752,191**
		UGT1A1 *1/*28	0.466	0	0.0000						
		UGT1A1 *28/*28	0.101	261	0.0024						
		UGT1A1 IM	0.002	0	0.0000						
		UGT1A1 PM	0.001	3	0.0024						
Mercaptopurine	2,177	*TPMT* EM	0.912	0	0.0000	4.9	4.2	**0.7 (14.5%)**	3,057	2 (fairly certain)	**160,309**
		TPMT IM	0.087	189	0.0036						
		TPMT PM	0.001	2	0.0097						
Tioguanine	2,854	*TPMT* EM	0.912	0	0.0000	6.5	5.5	**0.9 (14.5%)**	3,057	0 (very uncertain)	**385,084**
		TPMT IM	0.087	248	0.0036						
		TPMT PM	0.001	3	0.0097						
TOTAL	**148,128**	-	-	**35,762 (24.1%)**	**0.3**	**3,959**	**3,541**	**419 (10.6%)**	-	**2.5 (fairly certain)**	**51,187**

DGI = drug-gene interaction; PGx-guided = pharmacogenomics guided; RRR = relative risk reduction; GDR = gene-drug-related death; *$[N_{actionable\ DGI}]*[P_{phenotype}]*[N_{drug\ initiators}]$; †[absolute risk untested$_{phenotype}$]-[absolute risk tested$_{phenotype}$]; §$[N_{drug\ initiators}]/[NNG]$; ‡$1/(SUM_{DGI}[\text{absolute risk reduction}_{phenotype}]*[P_{phenotype}])$; ‖[total costs]/$[N_{deaths\ prevented}]$.

However, these DGIs were not considered "essential" by the DPWG and were therefore not included in our analysis. Consistent with individual DGIs investigated here, previous studies have shown the cost-effectiveness of *UGT1A1* for irinotecan dosing (38, 39), *CYP2C19* for clopidogrel dosing and alternative drug selection (40, 41), and *TPMT* guided initial dosing for thiopurines (42). Although a cost-minimization study for *DPYD* guided dosing has been performed (43, 44), its cost-effectiveness remains undetermined.

Model Design and Inputs

The outcome selected for this decision-analytic model is gene-drug-related death. This outcome excludes other, less severe, outcomes which may be improved by PGx-guided pharmacotherapy such as reduction in non-fatal ADRs or lack of drug efficacy. Excluding less severe but probably more prevalent gene-drug associated ADRs may therefore have resulted in an underestimation of the impact of PGx on patient outcomes. Taking these non-fatal ADRs into account would further confirm the cost-effectiveness of PGx-guided pharmacotherapy for "essential" DGIs. On the other side of the spectrum, while the PGx intervention decreases the risk of gene-drug associated ADRs, it may also increase risk of other negative effects such as loss of efficacy or increased risk for other ADRs. These are excluded from the current analysis and as a result we may have overestimated the (cost-)effectiveness. Regarding loss of efficacy, we expect equal drug exposures and benefit/risk among IMs and PMs receiving reduced doses and EMs receiving normal doses, as prospectively demonstrated (12). The extent to which efficacy may be compromised is largest in drugs with a steep dose-response curve and where the default population dose is not at maximum effect or saturated receptor occupancy (45). Therefore, we do not expect that excluding loss of efficacy has affected our overall results much since efficacy was included in the intermediate outcome (which was a composite of death, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) for the most predominant DGI (clopidogrel-*CYP2C19*). The potential underestimation from excluding potential other ADRs can be illustrated by ADRs associated with the PGx-guided treatment. For example, although *CYP2C19* guided treatment for clopidogrel dosing or alternative selection was non-inferior to treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events, treatment with ticagrelor or prasugrel resulted in higher incidence of minor bleeding (14). In this particular example, excluding minor bleeding from the mode has not affected the validity of our results, since minor bleeding do not result in drug-related death.

The time-horizon of the decision-analytic model was set at one year, consistent with the follow-up duration of the supporting trials. Ignoring impact beyond one year may have led to an underestimation of the benefit of the intervention. On the other hand, the imposed time-horizon overestimates the costs saved by the PGx intervention. In our current analysis we observed an overall cost increase for PGx-guided drug therapy when compared to standard of care which was driven by increased costs of PGx-guided alternatives for

clopidogrel (increased cost of €2.8 million per year). Since clopidogrel is used life-long after a Transient Ischemic Attack, the additional drug costs will increase with an increasing time horizon. Additionally, we did not take into account potential dose or drug changes which may have occurred within standard of care, in the absence of a PGx test. If these changes were to be made within this one year time-horizon there would be no additional effect relative to the PGx intervention. This may be the case for drugs, such as fluoropyrimidines and thiopurines which may be dosed in standard of care upon other biomarkers, such as hematological counts.

Potential factors limiting the generalizability of the model are the underlying assumptions made. Firstly, to facilitate absolute risk extraction, we assumed each of the drug initiators to have one particular indication (as described in **Appendix 3**) and to receive a corresponding standardized drug dose. However, some drugs included in the analysis can be applied for numerous indications. Patients with these other indications may have a different baseline risk of gene-drug-related death as a result of variation in general health or clinical monitoring. Additionally, the effectiveness of PGx-guided prescribing may also vary across indications due to different applied doses. For example, we performed risk extraction for thiopurines on publications including Inflammatory Bowel Disease patients. However, a minority of patients initiating thiopurines has other indications such as Acute Lymphatic Leukemia or Rheumatoid Arthritis, which are applied at lower doses and among patients who are monitored more closely for myelosuppression. Secondly, we assumed the ethnicity of the target population be Caucasian and therefore limited publication selection for absolute risk extraction to those performed in predominantly Caucasian samples. Since allele frequencies vary across ethnicities, we would be hesitant to extrapolate the reported results to ethnicities not included in the underlying publications. While for *TPMT* (46) allele frequencies are fairly constant across ethnicities, the frequency of actionable phenotypes are higher for *UGT1A1* in Blacks and Hispanics (47), *CYP2C19* in Asians (48) and *DPYD* in Africans (49) and therefore the current analysis underestimates cost-effectiveness in these ethnicities. Thirdly, the current model was constructed for the Netherlands. Since the effectiveness of the PGx intervention may be dependent on the quality of the health-care system we would be hesitant to extrapolate our results to counties with a different quality of health-care system. If both the healthcare system and ethnicity is similar, we would suggest extrapolating our results to other countries in proportion to the population size (17 million).

In this study, we estimated the number of drug initiators of the investigated seven drugs to be 148,128 per year, with 24.1% of initiators having an actionable DGI. A previous study estimated the number of drug initiators for 45 drugs with a DPWG recommendation in the Netherlands to be much higher at 3,628,597 new prescriptions per year, with a similar portion of those with actionable DGI (23.6% vs 24.1%) (27). This discrepancy is a result of the reported study using dispersion data from community pharmacies serving primary care. In contrast, our study used data encompassing primary and hospital care. Additionally, the

previous study excluded drugs only applied in hospital care such as capecitabine, fluorouracil, and irinotecan. However, similar numbers of drug initiators are reported to be applied both in primary and hospital settings: azathioprine (6,943 vs 6,979), clopidogrel (98,709 vs 117,900), mercaptopurine (2,598 vs 2,177) and thiopurine (1,883 vs 2,854). Despite a seemingly large discrepancy initially, these numbers confirm the accuracy of the number of yearly drug initiators in the presented model.

In the presented analysis, we limited the input of costs to PGx-testing, HCP interpretation, and drugs and thereby we have excluded the cost of hospitalization as a result of gene-drug-related ADRs which do not lead to death. Despite this limited perspective, we argue that we have been conservative in estimation of costs. For example, the cost of PGx tests were based on 2018 LUMC prices, which are higher than the current prices in 2020. This confirms the prediction that costs of genetic tests are decreasing. Although performed with a different PGx intervention and target population, PGx cost-savings have previously been estimated at $218 per tested patient (50). Additional cost-savings that were excluded are the reduced healthcare utilization resulting from reduced dose switching (51, 52) or reduced clinical monitoring (44). As a result, we are conservative in the cost of preventing gene-drug-related deaths and underestimate additional cost-saving.

Limitations

A key limitation of our approach is that the selected publications for risk of gene-related death extraction were powered on intermediate outcomes and not on drug-induced mortality (those corresponding to a certainty score 3 and lower). However, we do not expect PGx studies to be powered on mortality since these would require large sample sizes. As a result, we had to resort to the extraction of the absolute risk of intermediary outcomes, such as drug-induced myelosuppression, that are known to be associated with gene-drug-related death and multiplied this with the risk of mortality as a result of this intermediary outcome. While the extraction of the risk of mortality and intermediary outcomes was performed systematically based on literature underlying the DPWG, the risk of death as a result of intermediary outcomes was non-systematic, driven by the investigators' judgment of being suitable. Additionally, the majority of effect-sizes of PGx-guide prescribing to prevent gene-drug-related deaths are extracted from a number of observational studies. Ideally, these would be extracted from randomized controlled trials (RCTs) directly comparing PGx intervention to standard of care. However, we feel extraction from observational studies is substantiated since we do not expect RCTs to be performed for every individual DGI (53, 54).

Future research

The current study reports on seven "essential" DGIs in single-gene scenarios, but many more recommendations for actionable DGIs are available which intend to prevent non-fatal ADRs. From 2005 onwards the DPWG has developed recommendations for 54

actionable DGIs (17, 18) and in parallel, the CPIC has devised guidelines for over 40 drugs (16). In the near future, PGx delivery will shift from single-gene reactive model to a pre-emptive panel-testing model. Here, multiple pharmacogenes are tested simultaneously and recorded in the EMR in preparation of future prescriptions. Pre-emptive panel-testing may optimize both logistics and cost-effectiveness. This is supported by the observation that patients will receive multiple drug prescriptions with potential DGIs within their lifetime (55, 56) and the fact that marginal acquisition costs of testing and interpreting additional pharmacogenes is near-zero (20). However, the pre-emptive nature may also reduce cost-effectiveness, as not all tested individuals will actually benefit from the testing. Therefore, as implementation of PGx transitions from a single-gene approach to a pre-emptive panel approach, future efforts should quantify the cost-effectiveness of a panel of pharmacogenes to guide dose and drug selection of the remaining DGIs for which guidelines are available and over a longer time-horizon.

CONCLUSION

We used a decision-analytic model to assess the cost-effectiveness of nation-wide PGx-guided initial drug treatment for seven DGIs categorized as "essential" by the DPWG in the Netherlands. We found that nation-wide adoption of PGx-guided initial dose and drug selection of "essential" DGIs can potentially save the lives of 419 (0.3% of drug initiators) at reasonable costs (€51,000 per prevented death). The weighted average certainty score was 2.5 (fairly certain). These results support nation-wide adoption of PGx-guided initial drug treatment for "essential" DGIs.

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SUPPLEMENTARY MATERIAL

Appendix 1 Overview of the used initiator/user ratios and calculated number of drug initiators

Drug	Number of nation-wide users from GIP databank	N initiators in LUMC in 2018	N users + N initiators and users in LUMC in 2018	Ratio initiators/users	Calculated N drug initiators nation-wide
Azathioprine	26,153	317	1,188	0.267	26,153
Capecitabine	11,966	194	262	0.740	11,966
Clopidogrel	315,877	2,447	6,556	0.373	315,877
Fluorouracil (systemic + cutaneous)	54,815	442	1,110	-	-
Fluorouracil (cutaneous)	-	305	944	-	-
Fluorouracil (systemic)	8,198*	137	166	0.825	8,198
Irinotecan	2,593	48	0	1	2,593
Mercaptopurine	6,411	36	106	0.340	6,411
Tioguanine	5,116	82	147	0.558	5,116

*Calculated by multiplying with % systemic users in LUMC in 2018 (= N systemic users/ N systemic + N cutaneous users in 2018 = 166/1,110*100%=14.95%)

Appendix 2 Systematic methodology to select publications and extract absolute risk of gene-drug-related-death

The steps shown in Table 1 are performed systematically to select relevant publications from which to extract the absolute risk of gene-drug-related death. Risk extraction is performed by using methodology corresponding to that step. Each extracted absolute risk of death is given a certainty score based on the step in which publication(s) are selected.

The publication selection is performed systematically using only the publications listed in the summary of the systematic review of literature underlying the DPWG guideline ("the risk analysis"). Each of the publications listed in the risk analysis have been scored systematically by the DPWG both on the clinical relevance and on the quality of evidence [1]. The quality of evidence for each publication was scored on a five-point scale ranging from 0 (lowest quality of evidence) to 4 (highest quality of evidence). Score 4 corresponds to controlled, published studies of good quality or well-performed meta-analyses. Good quality is defined as: it is known whether comedication with an influence on the phenotype has been used; it is known whether other confounders are present (depending on the substance, for example smoking or not); the data are based on steady state kinetics; corrected for this at a variable dose [2]. Score 3 corresponds to controlled, published studies of moderate quality or poorly performed meta-analyses (for example, no good statistics, studies with different measured endpoints, heterogeneity, publication bias). Moderate quality is defined as: at least one of the criteria considered under good quality does not apply [2].

The risk of gene-drug-related death will vary across predicted phenotype groups. For example, risk of fluoropyrimidine-induced toxicity increases with decreasing *DPYD* gene activity scores (GAS), when all groups receive the same initial dose. Furthermore, when a PGx test is used to guide dose selection, those who have an actionable predicted phenotype (*DPYD* GAS 0-1.5) will have a reduced risk of fluoropyrimidine-induced toxicity when compared to risk when using a normal dose. The risk of death as a result of fluoropyrimidine-induced toxicity, however, in those with a non-actionable predicted phenotype (in this case *DPYD* GAS 2) will have the same risk, regardless of being PGx tested. Therefore, we will extract the absolute risk of death for each predicted phenotype category, across three groups: 1) tested-actionables (e.g. *DPYD* GAS 0, 0.5, 1 and 1.5 with PGx informed reduced dose), 2) non-actionables (e.g. *DPYD* GAS 2 with normal dose) and 3) untested-actionables (e.g. *DPYD* GAS 0, 0.5, 1 and 1.5 with normal dose). The predicted phenotype-gene interactions which are categorized as being actionable or non-actionable are provided in Table 1.

Other publications may be selected for extraction of each absolute risk. For example, risks of untested-actionables and non-actionables groups may be extracted from observational studies. However, the risks of tested-actionables group must be extracted from interventional studies. When a publication is selected for one of these three groups within one step but is not suitable for risk extraction of the remaining groups, the following step is performed to find a suitable publication for the remaining groups.

Table 1 Systematic methodology to select suitable publications and subsequent extraction of absolute risk of gene-drug-related-death within one year. The steps are executed consecutively until at least one suitable publication is found.

Step	Suitable publication(s)	Risk extraction method	1) tested actionables 2) non-actionables 3) untested actionables	Certainty Score
1	Publications reporting predicted phenotype group: quality score 4[a], powered on mortality	The risk of mortality of the most severe preventable clinical consequence within one year is extracted.		4 = Very certain
2	Publications reporting predicted phenotype group: quality score 4[a]	The risk of the intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. This is found by searching literature.		3 = Certain
3	Publications reporting predicted phenotype group: quality score 3[b], powered on mortality	The risk of mortality of the most severe preventable clinical consequence within one year is extracted.		2 = Fairly certain
4	Publications reporting predicted phenotype group: quality score 3[b]	The risk of the intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. This is found by searching literature.		1 = Uncertain
5	Perform literature review in review of a usable study regarding the relevant DGI	When the study is powered on mortality the risk of mortality within one year is extracted. When the study reported on an intermediary outcome, the intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. This is found by searching literature.		Based on quality score criteria of DPWG
6 No publication selected	Estimation			0 = Very uncertain

[a] Controlled, published studies of good quality with genotyping and / or phenotyping in patients / healthy subjects with clinical endpoints (effectiveness, side effects) or relevant kinetic endpoints (change in plasma level, AUC, half-life, etc.) or good performed meta-analyzes. Good quality is defined as: it is known whether comedication with an influence on the phenotype has been used; it is known whether other confounders are present (depending on the substance, for example smoking or not); the data are based on steady state kinetics; corrected for this at a variable dose [2]. [b] Controlled, published studies of moderate quality. with genotyping and / or phenotyping in patients / healthy subjects with clinical endpoints (effectiveness, side effects) or relevant kinetic endpoints (change in plasma level, AUC, half-life, etc.) or poor performed meta-analyzes (for example, no good statistics, studies with different measured endpoints, heterogeneity, publication bias). Moderate quality means that one or more of the items considered under good quality are missing [2].

Publication(s) selection

Publications are selected only if they present usable risk data and are sufficiently representative for the healthcare system and patients in the Netherlands. Being usable is defined as presenting risk data from which risks for at least one of the three groups can be calculated without requesting raw data underlying the publication. Being sufficiently representative is defined as studies including patients of which at least 50% are from North America or Europe.

Absolute risk extraction

Once at least one publication has been selected for each relevant drug-phenotype category for three patient groups: 1) tested-actionables, 2) non-actionables and 3) untested-actionables we are able to extract risks. This is performed corresponding to the step in which the publication was selected (see below).

Within a particular step, if only one publication is selected, the absolute risks of death are extracted from that single publication. When more than one publication is found suitable, the absolute risks of death are extracted from each publication and the mean is taken (weighed by the number of patients). However, when multiple meta-analyses are selected within one step, the risk extraction will only be performed based on the most recent meta-analysis, provided the majority of studies included in older meta-analyses.

Step 1: Publications reporting predicted phenotype group: quality score 4, powered on mortality (certainty score 4)

The risk of mortality of the most severe preventable clinical consequence within one year is extracted directly.

Step 2: Publications reporting predicted phenotype group: quality score 4, calculating the risk of death from intermediary outcome (certainty score 3)

The risk of an intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. Risk of death as a result of an intermediary outcome is found by searching literature and presented in Appendix 2 section "Assessment of risk of drug-related death following an intermediary outcome associated with the gene-drug interaction".

Step 3: Publications reporting predicted phenotype group: quality score 3, powered on mortality (certainty score 2)

The risk of mortality of the most severe preventable clinical consequence within one year is extracted.

Step 4: Publications reporting predicted phenotype group: quality score 3, calculating the risk of death from intermediary outcome (certainty score 1)

The risk of the intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. Risk of death as a result of an intermediary outcome is found by searching literature and presented in Appendix 2 section "Assessment of risk of drug-related death following an intermediary outcome associated with the gene-drug interaction".

Step 5: Perform literature review in review of a usable study regarding the relevant DGI (certainty score is based on quality of evidence criteria of DPWG)

When the study is powered on mortality the risk of mortality within one year is extracted. When the study reported on an intermediary outcome, the intermediary outcome within one year is extracted and is multiplied by the risk of death as a result of this intermediary outcome within one year. This is found by searching literature and presented in Appendix 2 section "Assessment of risk of drug-related death following an intermediary outcome associated with the gene-drug interaction".

Step 6: No publication selected: (certainty score 0 - estimation)
When none of the selected publications are intervention studies, we are unable to extract the risk of death for tested actionables. In this case we estimate the risk of death for tested actionables to equal the risk of death of non-actionables. In this case it is given a certainty score of 0 (estimation).

References Appendix

1. Swen JJ, Wilting I, de Goede AL, Grandia L, Mulder H, Touw DJ, et al. Pharmacogenetics: from bench to byte. Clinical pharmacology and therapeutics. 2008;83(5):781-7.
2. https://kennisbank.knmp.nl/files/farmacogenetica/Achtergrondteksten/fgbk.pdf

Appendix 3 Systematic selection of literature and extraction of absolute risk of gene-drug-related death

TPMT-AZATHIPURINE/MERCAPTOPURINE

Publication selection

Risk analysis: https://kennisbank.knmp.nl/files/farmacogenetica/1905-1906.PDF

Since the risk analysis is combined for both azathioprine and mercaptopurine, the publication selection and risk extraction will also be combined for both.

There is a DPWG guideline for the indications of acute lymphoblastic leukaemia (ALL) and irritable bowel syndrome (IBD). We have chosen to only select literature for application of *TPMT* guided prescribing for IBD. Reason for this being that the majority of patients initiating thiopurines have an IBD indication.

<table>
<tr><td></td><td>Steps performed systematically to select suitable publication(s) form which extraction is performed</td><td>Publication(s) selection</td></tr>
<tr><td>1</td><td>Publications reporting predicted phenotype group: quality score 4, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Relling MJ et al.(1)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lui C et al.(2)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Booth RA et al.(3)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Zelinkova Z et al.(4)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Fabre MA et al. (5)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Pandya B et al.(6)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Stanulla M et al.(7)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No literature was selected therefore we will continue to the next step.
</td></tr>
<tr><td>2</td><td>Publications reporting predicted phenotype group: quality score 4</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Relling MJ et al.(1)</td><td>Usable risk data: Yes
Representative: No, indication in this study is ALL patients.
Not selected.</td></tr>
<tr><td>Lui C et al.(2)</td><td>Representative: No, indication in this study is ALL patients.
Not selected.</td></tr>
<tr><td>Booth RA et al.(3)</td><td>Usable risk data: Yes
Representative: Yes
Selected for extraction of untested and non-actionable groups.</td></tr>
<tr><td>Zelinkova Z et al.(4)</td><td>Representative: Yes
Usable risk data: Yes
Not selected. (Data is included in included meta-analysis by Booth et al.)</td></tr>
<tr><td>Fabre MA et al. (5)</td><td>Representative: No, indication in kidney transplantation patients.
Not selected.</td></tr>
<tr><td>Pandya B et al.(6)</td><td>Representative: No, indication in kidney transplantation patients.
Not selected.</td></tr>
<tr><td>Stanulla M et al.(7)</td><td>Representative: No, indication in this study is ALL patients.
Not selected.</td></tr>
</table>
Conclusion:
Booth RA et al.(3) was selected for extraction of untested and non-actionable groups.
Therefore we will continue with the next step to obtain the data for the tested groups.
</td></tr>
<tr><td>3</td><td>Publications reporting predicted phenotype group: quality score 3, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Fan X et al. (8)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Choi R et al. (9)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Eriksen P et al. (10)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Coenen MJ et al. (11)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lennard L et al. (12)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lennard L et al. (13)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kim MJ et al. (14)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Leninsen M et al. (15)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
</td></tr>
</table>

		Kim H et al. (16)	Not powered on mortality. Not selected.
		Newman W et al. (17)	Not powered on mortality. Not selected.
		Dong XW et al. (18)	Not powered on mortality. Not selected.
		Hildorf U et al. (19)	Not powered on mortality. Not selected.
		Sheffiled L et al. (20)	Not powered on mortality. Not selected.
		Ansari A et al. (21)	Not powered on mortality. Not selected.
		Gardiner S et al. (22)	Not powered on mortality. Not selected.
		Moloney FJ et al. (23)	Not powered on mortality. Not selected.
		Jun JB et al. (24)	Not powered on mortality. Not selected.
		Stocco G et al. (25)	Not powered on mortality. Not selected.
		Kurzawski M et al. (26)	Not powered on mortality. Not selected.
		Gearry RB et al. (27)	Not powered on mortality. Not selected.
		Ansari A et al. (28)	Not powered on mortality. Not selected.
		Langley P et al. (29)	Not powered on mortality. Not selected.
		Regueiro M et al. (30)	Not powered on mortality. Not selected.
		Campbell S et al. (31)	Not powered on mortality. Not selected.
		Colombel JF et al. (32)	Not powered on mortality. Not selected.
		Black AJ et al. (33)	Not powered on mortality. Not selected.
		Higgs JE et al. (34)	Not powered on mortality. Not selected.
		Evans et al. (35)	Not powered on mortality. Not selected.
		McLeod HL et al. (36)	Not powered on mortality. Not selected.
		Conclusion: No literature was selected therefore we will continue to the next step.	
4	Publications reporting predicted phenotype group: quality score 3	**Study**	**Included in input data**
		Fan X et al. (8)	Representative: No, Chinese patients. Not selected.
		Choi R et al. (9)	Representative: No, Korean pediatric ALL patients. Not selected.
		Eriksen P et al. (10)	Representative: No, autoimmune hepatitis patients. Not selected.
		Coenen MJ et al. (11)	Representative: Yes Usable risk data: Yes **Selected for extraction of tested groups.**
		Lennard L et al. (12)	Representative: No, ALL patients. Not selected.
		Lennard L et al. (13)	Representative: No, ALL patients. Not selected.
		Kim MJ et al. (14)	Representative: No, Korean patients. Not selected.
		Leninsen M et al. (15)	Representative: No, ALL patients. Not selected.
		Kim H et al. (16)	Representative: No, ALL patients. Not selected.
		Newman W et al. (17)	Representative: Yes Usable risk data: No Not selected.
		Dong XW et al. (18)	Representative: No, less <50% of studies western. Not selected.
		Hildorf U et al. (19)	Representative: No, autoimmune hepatitis patients. Not selected.
		Sheffiled L et al. (20)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Ansari A et al. (21)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Gardiner S et al. (22)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Moloney FJ et al. (23)	Representative: No, renal transplant patients. Not selected.

		Jun JB et al. (24)	Representative: No, lupus erythematosus patients. Not selected.
		Stocco G et al. (25)	Representative: No, only pediatric patients. Usable risk data: No, not genotype-guided. Not selected.
		Kurzawski M et al. (26)	Representative: No, renal transplant patients. Not selected.
		Gearry RB et al. (27)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Ansari A et al. (28)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Langley P et al. (29)	Representative: No, autoimmune hepatitis patients. Not selected.
		Regueiro M et al. (30)	Representative: Yes Usable risk data: No Not selected.
		Campbell S et al. (31)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Colombel JF et al. (32)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Black AJ et al. (33)	Representative: No, rheumatic patients. Not selected.
		Higgs JE et al. (34)	Representative: No, not specific for IBD. Usable risk data: No, not genotype-guided. Not selected.
		Evans et al. (35)	Representative: No, ALL patients. Not selected.
		McLeod HL et al. (36)	Representative: No, ALL patients. Not selected.
		Conclusion: Coenen MJ et al. (11) was selected for extraction for tested-actionable groups.	
5	Perform literature review in review of a usable study regarding the relevant DGI	Not applicable	

Absolute risk extraction non-actionables (EM):

Booth RA et al.(3) was selected for extraction of non-actionables groups.

Booth RA et al.(3) is a meta-analysis of 31 studies into toxicity caused by azathioprine or mercaptopurine in a total of 3,638 patients with autoimmune diseases (including 260 IM and 19 PM). Leukopenia was the measure of outcome in 18 studies involving a total of 1,825 patients, including 105 IM and 7 PM.

Risk of leukopenia was 0.209573847 (See Appendix Figure 2, sum of events/sum of patients = 359/1713) among non-actionable TPMT EMs. Risk of death among IBD patients who develop myelotoxicity is approximately 0.01 (37). Therefore, risk of death as a result of leukopenia is 0.209573847 x 0.01 = 0.002095738 for non-actionable TPMT EMs. These are given a certainty score of 3.

Absolute risk extraction untested actionables (IM and PM):

Booth RA et al.(3) was selected for extraction of untested-actionables groups.

Booth RA et al. (3) is a meta-analysis of 31 studies into toxicity caused by azathioprine or mercaptopurine in a total of 3,638 patients with autoimmune diseases (including 260 IM and 19 PM). Leukopenia was the measure of outcome in 18 studies involving a total of 1,825 patients, including 105 IM and 7 PM.

TPMT IM:

Risk of leukopenia was 0.39047619 (See Appendix Figure 2, sum of events/sum of patients = 41/105) among untested-actionable TPMT IMs. Risk of death among IBD patients who develop myelotoxicity is approximately 0.01(37). Therefore, risk of death as a result of leukopenia is 0.39047619 x 0.01 = 0.003904762 for untested TPMT IMs. These are given a certainty score of 3.

TPMT PM:

The absolute number of leukopenia events is not presented for PMs. However, paragraph Enzyme Activity notes that the odds of leukopenia were significantly greater with low TPMT activity than with intermediate (OR= 2.74 [CI, 1.54 to 4.86]; 4 studies, 257 patients, and 91 events). Therefore the risk of leukopenia was calculated to be [untested-actionable TPMT IM = 0.39047619] X [OR of 2.74] = 1.069904 = 1. Risk of death among IBD patients who develop myelotoxicity is approximately 0.01(37). Therefore, risk of death as a result of leukopenia is 1 x 0.01 = 0.01 for untested TPMT PMs. These are given a certainty score of 3.

Absolute risk extraction tested actionables (IM and PM):

Coenen MJ et al. (11) was selected for extraction for tested-actionable groups. Coenen MJ et al. (11) is a randomized controlled trial. Here, 783 patients with IBD were treated with azathioprine (64% of patients) or 6-mercaptopurine (36% of patients). Follow-up was for a period of 20 weeks. Genotype-guided (*TPMT* *2, *3A and *3C) treatment (n = 405) was compared to standard treatment (n = 378). In the genotype-guided group, EMs received the normal thiopurine dose and IMs 50% of the normal dose. PM were scheduled to receive 0-10% of the normal dose. Hematologic adverse events were defined as leukocyte count < 3.0x109/L or platelet count < 100x109/L.A significantly smaller proportion of carriers of the TPMT variants in the intervention group (2.6%) developed hematologic ADRs compared with patients in the control group (22.9%) (relative risk, 0.11; 95% confidence interval, 0.01-0.85).

TPMT IM and PM:

Coenen et al. has combined the *TPMT* IMs and PMs in one group, therefore we will also perform risk extraction for IM and PMs combined. Risk of hematologic adverse events was 0.025641026 among tested TPMT IMs and PMs (1 event among 39 patients, see Table 3). Risk of death among IBD patients who develop myelotoxicity is approximately 0.01 (37). Therefore, risk of death as a result of leukopenia is 0.025641026 x 0.01 = 0.025641026 for tested TPMT IMs and PMs. These are given a certainty score of 1.

Conclusion of selected publications and absolute risks extracted:

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Azathiopurine/ Mercaptopurine	TPMT EM	no	0.002095738	(3)	3	0.002095738	(3)	3
Azathiopurine/ Mercaptopurine	TPMT IM	yes	0.003904762	(3)	3	0.00025641	(11)	1
Azathiopurine/ Mercaptopurine	TPMT PM	yes	0.01	(3)	3	0.00025641	(11)	1

Ref: Reference; CS: Certainty score

TPMT-TIOGUANINE

Publication selection

Risk analysis: https://kennisbank.knmp.nl/files/farmacogenetica/1907-1908.PDF

<table>
<tr><td></td><td>Steps performed systematically to select suitable publication(s) form which extraction is performed</td><td>Publication(s) selection</td></tr>
<tr><td>1</td><td>Publications reporting predicted phenotype group: quality score 4, powered on mortality</td><td>There are no studies available through the “risk analysis” that have a quality score of 4.
Conclusion:
No literature was selected therefore we will continue to the next step.</td></tr>
<tr><td>2</td><td>Publications reporting predicted phenotype group: quality score 4</td><td>There are no studies available through the “risk analysis” that have a quality score of 4.
Conclusion:
No literature was selected therefore we will continue to the next step.</td></tr>
<tr><td>3</td><td>Publications reporting predicted phenotype group: quality score 3, powered on mortality</td><td><table><tr><th>Study</th><th>Conclusion</th></tr><tr><td>Lennard L et al. (13)</td><td>Not powered for mortality</td></tr><tr><td>Wray L et al. (38)</td><td>Not powered for mortality</td></tr><tr><td>Lennard L et al. (39)</td><td>Not powered for mortality</td></tr><tr><td>Teml A et al. (40)</td><td>Not powered for mortality</td></tr><tr><td>Herrlinger KR et al.(41)</td><td>Not powered for mortality</td></tr></table>Conclusion:
No literature was selected therefore we will continue to the next step.</td></tr>
<tr><td>4</td><td>Publications reporting predicted phenotype group: quality score 3</td><td><table><tr><th>Study</th><th>Conclusion</th></tr><tr><td>Lennard L et al. (13)</td><td>Usable risk data: No</td></tr><tr><td>Wray L et al. (38)</td><td>Usable risk data: No
Patients are children with ALL.</td></tr><tr><td>Lennard L et al. (39)</td><td>Usable risk data: No
Patients are children with ALL.</td></tr><tr><td>Teml A et al. (40)</td><td>Usable risk data: No. Very small study population.</td></tr><tr><td>Herrlinger KR et al.(41)</td><td>Usable risk data: No. Very small study population.</td></tr></table>Conclusion:
No literature was selected therefore we will continue to the next step.</td></tr>
<tr><td>5</td><td>Perform literature review in review of a usable study regarding the relevant DGI</td><td><table><tr><th>Search strategy pubmed</th><th>Date literature search</th></tr><tr><td>(Thioguanine[Title] OR Tioguanine[Title] OR 6-thioguanine[Title] OR 6-TG[Title]) AND (TPMT[Title] OR Thiopurine[Title] OR Pharmacogenetic[Title] OR Pharmacogenetics [Title] OR genotype[Title] OR genotypes[Title] OR polymorphism[Title] OR polymorphisms[Title])</td><td>02-12-2019</td></tr></table>Conclusion:
We found no additional studies through our own literature search. Therefore, we estimated the absolute risk on death for thioguanine to be similar to azathioprine and 6-mercaptopurine. The certainty score given is 0, since it is an estimation.</td></tr>
</table>

Conclusion of selected publications and absolute risks extracted:

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Thioguanine	TPMT EM	no	0.002095738	(3)	0	0.002095738	(3)	0
Thioguanine	TPMT IM	yes	0.003904762	(3)	0	0.00025641	(11)	0
Thioguanine	TPMT PM	yes	0.01	(3)	0	0.00025641	(11)	0

DPYD-CAPECITABINE/5-FU

Publication selection

Risk analysis: https://kennisbank.knmp.nl/files/farmacogenetica/2552-4893-4894.PDF

Since the risk analysis is combined for both capecitabine and 5-FU, the publication selection and risk extraction will also be combined for both.

<table>
<tr><td></td><td>Steps performed systematically to select suitable publication(s) form which extraction is performed</td><td>Publication(s) selection</td></tr>
<tr><td>1</td><td>Publications reporting predicted phenotype group: quality score 4, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Deenen MJ et al. (42)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Meulendijks D et al. (43)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Meulendijks D et al.(44)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Rosmarin D et al.(45)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Terrazzino S et al. (46)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Vulsteke C et al. (47)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No publication was selected therefore we will continue to the next step.
</td></tr>
<tr><td>2</td><td>Publications reporting predicted phenotype group: quality score 4</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Deenen MJ et al. (42)</td><td>Usable risk data: Yes (includes alleles relevant for Dutch population)
Representative: Yes
Not selected. (Study is present in the included meta-analysis by Meulendijks et al. (44))</td></tr>
<tr><td>Meulendijks D et al. (43)</td><td>Usable risk data: Yes
Representative: No. Study only in small population for specific alleles.
Not selected.</td></tr>
<tr><td>Meulendijks D et al.(44)</td><td>Usable risk data: Yes
Representative: Yes
Selected for extraction of untested groups.</td></tr>
<tr><td>Rosmarin D et al.(45)</td><td>Usable risk data: No
Representative: Yes
Not selected.</td></tr>
<tr><td>Terrazzino S et al. (46)</td><td>Usable risk data: Yes
Representative: Yes
Not selected. Another meta-analysis is more recent.</td></tr>
<tr><td>Vulsteke C et al. (47)</td><td>Usable risk data: Yes.
Representative: Yes
Not selected. Another meta-analysis is more recent.</td></tr>
</table>
Conclusion:
Meulendijks D et al.(44) was selected for extraction of untested and non-actionable groups. Therefore we will continue with the next step to obtain the data for the tested groups..
</td></tr>
<tr><td>3</td><td>Publications reporting predicted phenotype group: quality score 3, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Kleinjan JP et al.(48)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Henricks LM et al. (49)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lunenburg CATC et al. (50)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Henricks LM et al.(51)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Madi A et al. (52)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lunenburg CA et al.(53)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lee AM et al. (54)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Deenen MJ et al. (55)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lee AM et al. (56)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>van Kuilenburg AB et al.(57)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kristensen MH et al.(58)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Gross E et al.(59)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Capitain O et al. (60)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
</td></tr>
</table>

		Sulzyc-Bielicka V et al.(61)	Not powered on mortality. Not selected.
		Schwab M et al. (62)	Not powered on mortality. Not selected.
		Mercier C et al.	Not powered on mortality. Not selected.
		Jatoi A et al.(63)	Not powered on mortality. Not selected.
		Magné N et al. (64)	Not powered on mortality. Not selected.
		Boisdron-Celle M et al. (65)	Not powered on mortality. Not selected.
		Cho HJ et al. (66)	Not powered on mortality. Not selected.
		Salgado J et al. (67)	Not powered on mortality. Not selected.
		Morel A et al. (68)	Not powered on mortality. Not selected.
		Largillier R et al. (69)	Not powered on mortality. Not selected.
		Salgueiro N et al. (70)	Not powered on mortality. Not selected.
		Van Kuilenburg AB et al.(71)	Not powered on mortality. Not selected.
		Raida M et al. (72)	Not powered on mortality. Not selected.
		Yamaguchi K et al. (73)	Not powered on mortality. Not selected.
		van Kuilenburg AB et al.(74)	Not powered on mortality. Not selected.
		Conclusion: No publications were selected therefore we will continue to the next step.	
4	Publications reporting predicted phenotype group: quality score 3	**Study**	**Conclusion**
		Kleinjan JP et al.(48)	Representative: Yes, Dutch population. Usable risk data: Yes **Selected for extraction of tested groups.**
		Henricks LM et al. (49)	Representative: Yes, Dutch population. Usable risk data: Yes **Selected for extraction of tested groups.**
		Lunenburg CATC et al. (50)	Representative: Yes, Dutch population. Usable risk data: Yes **Selected for extraction of tested groups.**
		Henricks LM et al.(51)	Representative: Yes Usable risk data: Yes **Selected for extraction of tested groups.**
		Madi A et al. (52)	Usable risk data: no risk for tested actionables reported. Not selected.
		Lunenburg CA et al.(53)	Representative: Yes , Dutch population. Usable risk data: No Not selected.
		Lee AM et al. (54)	Usable risk data: no risk for tested actionables reported. Not selected.
		Deenen MJ et al. (55)	Representative: Yes, Dutch population. Usable risk data: Yes **Selected for extraction of tested groups.**
		Lee AM et al. (56)	Usable risk data: no risk for tested actionables reported. Not selected.
		van Kuilenburg AB et al.(57)	Representative: Yes, Dutch population. Usable risk data: No, not genotype-guided. Not selected.
		Kristensen MH et al.(58)	Usable risk data: no, not genotype-guided. Not selected.
		Gross E et al.(59)	Usable risk data: No, not genotype-guided. Not selected.
		Capitain O et al. (60)	Usable risk data: No, not genotype-guided. Not selected.
		Sulzyc-Bielicka V et al.(61)	Usable risk data: No, not genotype-guided. Not selected.
		Schwab M et al. (62)	Usable risk data: No, not genotype-guided. Not selected.
		Mercier C et al.	Representative: Yes Usable risk data: No Not selected.
		Jatoi A et al.(63)	Representative: Yes Usable risk data: No Not selected.

		Magné N et al. (64)	Representative: Yes Usable risk data: No Not selected.
		Boisdron-Celle M et al. (65)	Usable risk data: No, not genotype-guided. Representative: Yes Not selected.
		Cho HJ et al. (66)	Representative: No. Study is done in Korean population. Not selected.
		Salgado J et al. (67)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Morel A et al. (68)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Largillier R et al. (69)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Salgueiro N et al. (70)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Van Kuilenburg AB et al.(71)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Raida M et al. (72)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Yamaguchi K et al. (73)	Representative: No. Study is done in Japanese population. Not selected.
		van Kuilenburg AB et al.(74)	Representative: Yes Usable risk data: No, not genotype-guided. Not selected.
		Conclusion: We have selected 5 studies to extract the data for the tested groups: Kleinjan JP et al.(48) Henricks LM et al.(49) Lunenburg CATC et al. (50) Henricks LM et al.(51) Deenen M et al.(55)	
5	Perform literature review in review of a usable study regarding the relevant DGI	Not applicable	

Absolute risk extraction non-actionables (GAS 2):

Meulendijks D et al.(44) was selected for extraction of non-actionables groups.

Meulendijks D et al.(44) is a meta-analysis of 8 cohort studies with in total 7365 patients treated with 5-fluorouracil or capecitabine, either as combined chemotherapy (different combinations) or as monotherapy (with or without radiotherapy). Data on *13 were derived from 5 studies including a total of 5,616 patients and 11 carriers of *13. Data on 1236G>A were derived from 6 studies including a total of 4,261 patients and 174 heterozygous carriers and 3 homozygous carriers of 1236A. Data on *2A were derived from 7 studies including a total of 5.737 patients and 60 carriers of *2A. Data on 2846 A>T were derived from all 8 studies including a total of 7,318 patients and 85 carriers of 2846T.

Risk of grade 3 or higher fluoropyrimidine induced toxicity was 0.324008855 (See Figure 2, sum of events/sum of patients =6440/19876) among non-actionable DPYD GAS 2.0. Risk of death as a result of grade 3 or higher fluoropyrimidine induced toxicity is approximately 0.0075 (75). Therefore, risk of death as a result of leukopenia is 0.324008855 x 0.0075 = 0.002430066 for non-actionable DPYD GAS 2.0. These are given a certainty score of 3.

Absolute risk extraction untested actionables (GAS 0-1.5):

Meulendijks D et al.(44). was selected for extraction of untested-actionable groups.

Meulendijks D et al.(44) is a meta-analysis of 8 cohort studies with in total 7365 patients treated with 5-fluorouracil or capecitabine, either as combined chemotherapy (different combinations) or as monotherapy (with or without radiotherapy). Data on *13 were derived from 5 studies including a total of 5,616 patients and 11 carriers of *13. Data on 1236G>A were derived from 6 studies including a total of 4,261 patients and 174 heterozygous carriers and 3 homozygous carriers of 1236A. Data on *2A were derived from 7 studies including a total of 5.737 patients and 60 carriers of *2A. Data on 2846 A>T were derived from all 8 studies including a total of 7,318 patients and 85 carriers of 2846T.

GAS 1.5 (*1/c.1236G>A or *1/c.2846A>T):

Risk of grade 3 or higher fluoropyrimidine induced toxicity was 0.450381679 (See Figure 2 and Figure 4, (sum of events c.1236 + sum of events c.2846)/(sum of patients c.1236 + sum of patients c.2846) =(53+65)/(177+85)= 0.450381679) among untested-actionable DPYD GAS 1.5. Risk of death as a result of grade 3 fluoropyrimidine induced toxicity is approximately 0.0075 (75). Therefore, risk of death as a result of leukopenia is 0.450381679 x 0.0075 = 0.003377863 for untested-actionable DPYD GAS 1.5. These are given a certainty score of 3.

GAS 1.0 (*1/*2A or *1/*13):

Risk of grade 3 or higher fluoropyrimidine induced toxicity was 0.690140845 (See Figure 2 and Figure 4, sum of events *2A + sum of events *13)/(sum of patients *2A + sum of patients *13 = (43+6)/(60+11)) among untested-actionable DPYD GAS 1.0. Risk of death as a result of grade 3 fluoropyrimidine induced toxicity is approximately 0.0075 (75). Therefore, risk of death as a result of leukopenia is 0.690140845 x 0.0075 = 0.005176056 for untested-actionable DPYD GAS1.0. These are given a certainty score of 3.

GAS 0.5 (e.g. c.1236G>A/c.2846A>T or combinations of c.2846A>T or c.1236G>A with *2A or *13, example given *2A/c.2846A>T):

Risk of grade 3 or higher fluoropyrimidine induced toxicity was unable to be extracted for untested-actionable DPYD GAS 0.5 from Meulendijks D et al.(44). No suitable publication was identity in steps 3 or 4. Therefore we will assume the risk of grade 3 or higher fluoropyrimidine induced toxicity to increase linearly with decreasing GAS. Delta risk of death between GAS 1.5 and GAS 1.0 was 0.005176056 -0.003377863 = 0.0018. Therefore we estimate the risk of grade 3 or higher fluoropyrimidine induced toxicity for GAS 0.5 to be 0.005176056 – 0.0018 = 0.0034. Therefore we estimate the risk of grade 3 or higher fluoropyrimidine induced toxicity for GAS 0.5 to be [risk of death GAS 1.5 + delta risk] = 0.005176056 + 0.0018 = 0.0070. These are given a certainty score of 0

GAS 0 (*2A/*2A or *13/*13 or *2A/*13):

Risk of grade 3 or higher fluoropyrimidine induced toxicity was unable to be extracted for untested-actionable DPYD GAS 0. from Meulendijks D et al.(44). No suitable publication was identified in steps 3 or 4. Therefore we will assume the risk of grade 3 or higher fluoropyrimidine induced toxicity to increase linearly with decreasing GAS. Delta risk of death between GAS 1.5 and GAS 1.0 was 0.005176056 -0.003377863 = 0.0018. Therefore we estimate the risk of grade 3 or higher fluoropyrimidine induced toxicity for GAS 0.5 to be [risk of death GAS 0.5 + delta risk] = 0.0070 + 0.0018 = 0.0088. These are given a certainty score of 0.

Absolute risk extraction tested actionables (GAS 0-1.5):

Kleinjan JP et al.(48), Henricks LM et al. (49),Lunenburg CATC et al. (50), Henricks LM et al. (51), and Deenen M et al. (55) were selected for extraction of tested-actionable groups. Only patients who receive pre-therapeutic DPYD guided fluoropyrimidine therapy were considered for risk extraction.

Kleinjan JP et al.(48) is an observational study where capecitabine was dosed based on DPYD genotype in heterozygote DPYD variant carriers. Capecitabine doses were reduced in case of a DPYD variant (DPYD*2A, c.2846A>T, DPYD*13, or c.1236G>A) and subsequently adjusted on the basis of tolerance. Results were compared with a cohort of capecitabine-treated DPYD wild-type patients. Of 185 patients eligible for analysis, 11 patients were heterozygous for a DPYD variant. A median dose escalation of 8.5% was achieved using the prespecified protocol. One DPYD variant carrier experienced a grade 3 toxicity after a dose escalation. Overall, DPYD variant carriers did not experience more, or more severe toxicities than DPYD wild-type patients. The total prevalence of severe toxicities in the wild-type group was 43.1% and is comparable with the literature.

Henricks LM et al.(49) investigated the effectiveness and safety of DPYD*2A genotype-guided dosing. A cohort of 40 prospectively identified heterozygous DPYD*2A carriers, treated with a ~50% reduced fluoropyrimidine dose, was identified. The frequency of severe (grade ≥ 3) treatment-related toxicity was compared to 1] a cohort of 1606 wild-type patients treated with full dose and 2] a cohort of historical controls derived from literature, i.e. 86 DPYD*2A variant carriers who received a full fluoropyrimidine dose. For 37 out of 40 DPYD*2A carriers, a matched control could be identified. Compared to matched controls, risk of severe fluoropyrimidine-related toxicity in DPYD*2A carriers treated with reduced dose was 18%, comparable to wild-type patients (23%, p = 0.57) and significantly lower than the risk of 77% in DPYD*2A carriers treated with full dose (p < 0.001).40 patients with genotype *1/*2A and treated with an approximately 50% reduced fluoropyrimidine dose were compared

to patients without *2A and to *1/*2A treated with full dose. To compare safety, *1/*2A patients treated with a reduced dose were compared with 1606 patients without *2A treated with full dose from Deenen 2016 and with 86 historical controls (*2A-carriers treated with full dose; including the historical controls in Deenen 2016).

Lunenburg CATC et al. (50) investigated the risk of severe toxicity in DPYD variant allele carriers receiving chemoradiation. Medical records of 828 patients who received fluoropyrimidine based chemoradiation (FP-based CRT) were reviewed from three centres. Severe (grade ≥III) toxicity in DPYD variant allele carriers receiving upfront dose reductions according to pharmacogenetic dosing guidelines and DPYD variant allele carriers not receiving dose reductions was compared with DPYD wild-type patients receiving standard dose. DPYD variant allele carriers treated with standard dosages (N = 34) showed an increased risk of severe gastrointestinal (adjusted OR = 2.58, confidence interval [CI] = 1.02-6.53, P = 0.045) or severe haematological (adjusted OR = 4.19, CI = 1.32-13.25, P = 0.015) toxicity compared with wild-type patients (N = 771). DPYD variant allele carriers who received dose reductions (N = 22) showed a comparable frequency of severe gastrointestinal toxicity compared with wild-type patients, but more (not statistically significant) severe haematological toxicity. Hospitalisations for all DPYD variant allele carriers were comparable, independent of dose adjustments; however, the mean duration of hospitalisation was significantly shorter in the dose reduction group (P = 0.010).

Henricks LM et al.(51) is a prospective, multicentre, safety analysis in 17 hospitals in the Netherlands, the study population consisted of adult patients (≥18 years) with cancer who were intended to start on a fluoropyrimidine-based anticancer therapy (capecitabine or fluorouracil as single agent or in combination with other chemotherapeutic agents or radiotherapy). Patients with all tumour types for which fluoropyrimidine-based therapy was considered in their best interest were eligible. We did prospective genotyping for DPYD*2A, c.2846A>T, c.1679T>G, and c.1236G>A. Heterozygous DPYD variant allele carriers received an initial dose reduction of 25% (c.2846A>T and c.1236G>A) or 50% (DPYD*2A and c.1679T>G), and DPYD wild-type patients were treated according to the current standard of care. The primary endpoint of the study was the frequency of severe (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 grade ≥3) overall fluoropyrimidine-related toxicity across the entire treatment duration. Toxicity incidence was compared between DPYD variant allele carriers and DPYD wild-type and relative risks (RRs) for severe toxicity were compared between the current study and a historical cohort of DPYD variant allele carriers treated with full dose fluoropyrimidine-based therapy (derived from a previously published meta-analysis). Of 1103 evaluable patients, 85 (8%) were heterozygous DPYD variant allele carriers, and 1018 (92%) were DPYD wild-type patients. Overall, fluoropyrimidine-related severe toxicity was higher in DPYD variant carriers (33 [39%] of 85 patients) than in wild-type patients (231 [23%] of 1018 patients; p=0·0013). The RR for severe fluoropyrimidine-related toxicity was 1·31 (95% CI 0·63-2·73) for genotype-guided dosing compared with 2·87 (2·14-3·86) in the historical cohort for DPYD*2A carriers, no toxicity compared with 4·30 (2·10-8·80) in c.1679T>G carriers, 2·00 (1·19-3·34) compared with 3·11 (2·25-4·28) for c.2846A>T carriers, and 1·69 (1·18-2·42) compared with 1·72 (1·22-2·42) for c.1236G>A carriers.

Deenen M et al.(55) determines the feasibility, safety, and cost of DPYD*2A genotype-guided dosing. Patients intended to be treated with fluoropyrimidine-based chemotherapy were prospectively genotyped for DPYD*2A before start of therapy. Variant allele carriers received an initial dose reduction of ≥ 50% followed by dose titration based on tolerance. Toxicity was the primary end point and was compared with historical controls (ie, DPYD*2A variant allele carriers receiving standard dose described in literature) and with DPYD*2A wild-type patients treated with the standard dose in this study.

A total of 2,038 patients were prospectively screened for DPYD*2A, of whom 22 (1.1%) were heterozygous polymorphic. DPYD*2A variant allele carriers were treated with a median dose-intensity of 48% (range, 17% to 91%). The risk of grade ≥ 3 toxicity was thereby significantly reduced from 73% (95% CI, 58% to 85%) in historical controls (n = 48) to 28% (95% CI, 10% to 53%) by genotype-guided dosing (P < .001); drug-induced death was reduced from 10% to 0%. Adequate treatment of genotype-guided dosing was further demonstrated by a similar incidence of grade ≥ 3 toxicity compared with wild-type patients receiving the standard dose (23%; P = .64) and by similar systemic fluorouracil (active drug) exposure.

GAS 1.5 (*1/c.1236G>A or *1/c.2846A>T):

	Kleinjan JP et al.(48)*	Henricks LM et al.(49)	Lunenburg CATC et al. (50)	Henricks LM et al.(51)	Deenen M et al.(55)	Total
Number of patients GAS 1.5	11	Not reported	12	51+17=68	Not reported	91
Number of events	3	Not reported	5	3+1=4	Not reported	12
Overall absolute risk	-	-	-	-	-	0.131868

*Four (36.4%) were DPYD*2A heterozygous, one (9.1%) was c.2846A >T heterozygous, and the remaining six (54.5%) were c.1236G > A heterozygous. No DPYD*13 variant carriers were identified.

Risk of death as a result of grade 3 fluoropyrimidine induced toxicity is approximately 0.0075 (75). Therefore, risk of death as a result of leukopenia is 0.131868 x 0.0075 = 0.0010 for untested-actionable DPYD GAS 1.5. These are given a certainty score of 1.

GAS 1.0 (*1/*2A or *1/*13):

	Kleinjan JP et al.(48)*	Henricks LM et al.(49)	Lunenburg CATC et al. (50)	Henricks LM et al.(51)**	Deenen M et al.(55)	Total
Number of patients GAS 1.0	11	40	11	16+1=17	18	97
Number of events	3	7	5	0	2	17
Overall absolute risk	-	-	-	-	-	0.175258

*Four (36.4%) were DPYD*2A heterozygous, one (9.1%) was c.2846A >T heterozygous, and the remaining six (54.5%) were c.1236G > A heterozygous. No DPYD*13 variant carriers were identified.

**Only limit to prospectively genotyped patient for *2A, exclude historical controls from Deenen et al.

Risk of death as a result of grade 3 fluoropyrimidine induced toxicity is approximately 0,0075 (75). Therefore, risk of death as a result of leukopenia is 0.175258 x 0.0075 = 0.0013 for untested-actionable DPYD GAS 1.0. These are given a certainty score of 1.

GAS 0.5 (e.g. c.1236G>AA/c.2846A>T or combinations of c.2846A>T or c.1236G>A with *2A or *13, example given *2A/c.2846A>T):

	Kleinjan JP et al.(48)	Henricks LM et al.(49)	Lunenburg CATC et al. (50)	Henricks LM et al.(51)	Deenen M et al.(55)	Total
Number of patients GAS 0.5	Not reported	Not reported	Not reported	Not reported	Not reported	Not applicable
Number of events	Not reported	Not reported	Not reported	Not reported	Not reported	Not applicable
Overall absolute risk	-	-	-	-	-	Not applicable

Risk of grade 3 or higher fluoropyrimidine induced toxicity was unable to be extracted for untested-actionable DPYD GAS 0.5 from (48) (49, 50) (51, 55). No suitable publication was identified in step 5. Therefore we will assume the risk of grade 3 or higher fluoropyrimidine induced toxicity is equal to the mean risk of death of GAS 1.5 and 1. The mean of these is 0.0012. These are given a certainty score of 0.

GAS 0.0 (*2A/*2A or *13/*13 or *2A/*13):

	Kleinjan JP et al.(48)	Henricks LM et al.(49)	Lunenburg CATC et al. (50)	Henricks LM et al.(51)	Deenen M et al.(55)	Total
Number of patients GAS 0	Not reported	Not reported	Not reported	Not reported	Not reported	Not applicable
Number of events	Not reported	Not reported	Not reported	Not reported	Not reported	Not applicable
Overall absolute risk	-	-	-	-	-	Not applicable

Risk of grade 3 or higher fluoropyrimidine induced toxicity was unable to be extracted for untested-actionable DPYD GAS 0.5 from (48) (49, 50) (51, 55). No suitable publication was identified in step 5. Therefore we will assume the risk of grade 3 or higher fluoropyrimidine induced toxicity is equal to the mean risk of death of GAS 1.5 and 1. The mean of these is 0.0012. These are given a certainty score of 0.

Conclusion of selected publications and absolute risks extracted:

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Capecitabine/5-FU	DPYD GAS 0	yes	0.0088	-	0	0.0012	-	0
Capecitabine/5-FU	DPYD GAS 0.5	yes	0.0070	-	0	0.0012	-	0

Capecitabine/5-FU	DPYD GAS 1.0	yes	0.005176056	(44)	3	0.0013	(48) (49, 50) (51, 55)	1
Capecitabine/5-FU	DPYD GAS 1.5	yes	0.003377863	(44)	3	0.0010	(48) (50) (51)	1
Capecitabine/5-FU	DPYD GAS 2	no	0.002430066	(44)	3	0.002430066	(44)	3

Ref: Reference; CS: Certainty score

CYP2C19-CLOPIDOGREL

Publication selection

Risk analysis: https://kennisbank.knmp.nl/files/farmacogenetica/2548-2549-2550.PDF

There is a DPWG guideline for the combined indications of percutaneous coronary intervention (PCI), stoke and transient ischemic attack (TIA). Therefore, we have chosen to select publications and perform subsequent risk extraction for all three indications combined.

<table>
<tr><td></td><td>Steps performed systematically to select suitable publication(s) form which extraction is performed</td><td>Publication(s) selection</td></tr>
<tr><td>1</td><td>Publications reporting predicted phenotype group: quality score 4, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Niu X et al. (76)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Jang JS et al. (77)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Pan Y et al. (78)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Sorich MJ et al. (79)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Mao L et al. (80)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Li Y et al. (81)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Holmes MV et al. (82)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Liu YP et al. (83)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Mega JL et al.(84)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Simon T et al. (85)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Collet JP et al. (86)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Simon T et al. (87)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Shen DL et al. (88)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Mega JL et al.(89)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Geisler T et al.(90)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Chen BL et al.(91)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kim KA et al. (92)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Malek LA et al.(93)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Trenk D et al. (94)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Fontana P et al.(95)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Hulot JS et al.(96)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No publication was selected therefore we will continue to the next step.
</td></tr>
<tr><td>2</td><td>Publications reporting predicted phenotype group: quality score 4</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Niu X et al. (76)</td><td>Usable risk data: Yes
Representative: No, predominantly studies performed in Asia
Not selected.</td></tr>
<tr><td>Jang JS et al. (77)</td><td>Usable risk data: Yes (genetic variant in most studies is *2)
Representative: Yes
Not selected. Another meta-analysis is more recent (2012).</td></tr>
<tr><td>Pan Y et al. (78)</td><td>Usable risk data: Yes (*2, 3, 17, 1)
Representative: No
Not selected.</td></tr>
<tr><td>Sorich MJ et al. (79)</td><td>Usable risk data: Yes (*2, 3, 17, 1)
Representative: Yes
Most recent meta-analysis (2014). Selected for extraction of untested groups.</td></tr>
<tr><td>Mao L et al. (80)</td><td>Usable risk data: Yes (loss of function *2-*8)
Representative: Yes
Another meta-analysis is more recent (2013).</td></tr>
<tr><td>Li Y et al. (81)</td><td>Usable risk data: No (only *17)
Representative: Yes
Not selected.</td></tr>
<tr><td>Holmes MV et al. (82)</td><td>Usable risk data: Yes (any loss of function allele)
Representative: Yes</td></tr>
</table>
</td></tr>
</table>

			Not selected. Another meta-analysis is more recent (2011).
		Liu YP et al. (83)	Usable risk data: Yes (Any loss of function allele) Representative: Yes Not selected. Another meta-analysis is more recent (2011).
		Mega JL et al.(84)	Usable risk data: Yes (only *2 loss of function) Representative: Yes Not selected. Another meta-analysis is more recent.
		Simon T et al. (85)	Usable risk data: No Representative: No (healthy subjects) Not selected.
		Collet JP et al. (86)	Usable risk data: Yes (only *2 loss of function) Representative: No, young patients (<45 years) Not selected.
		Simon T et al. (87)	Usable risk data: Yes (multiple loss of function alleles) Representative: Yes Not selected. Included in meta-analysis by Sorich MJ et al.
		Shen DL et al. (88)	Representative: No, Chinese population. Not selected.
		Mega JL et al.(89)	Usable risk data: Yes Representative: Yes Not selected. Included in meta-analysis by Sorich MJ et al.
		Geisler T et al.(90)	Usable risk data: No Not selected.
		Chen BL et al.(91)	Representative: No, healthy volunteers Not selected.
		Kim KA et al. (92)	Representative: No, healthy volunteers Not selected.
		Malek LA et al.(93)	Representative: Yes Usable risk data: No, reports on CADP-CT
		Trenk D et al. (94)	Representative: Yes Usable risk data: No, reports on residual platelet aggregation
		Fontana P et al.(95)	Representative: No, healthy volunteers Not selected.
		Hulot JS et al.(96)	Representative: No, healthy volunteers. Not selected.
		Conclusion: Only the risks for the untested groups can be obtained with this step. We have selected the most recent suitable meta-analysis by Sorich MJ et al. (79) for extraction of data for untested groups.	
3	Publications reporting predicted phenotype group: quality score 3, powered on mortality	**Study**	**Conclusion**
		Lee CR et al.(97)	Not powered on mortality. Not selected.
		Zhong Z et al. (98)	Not powered on mortality. Not selected.
		Wu Y et al. (99)	Not powered on mortality. Not selected.
		Cavallari LH et al. (100)	Not powered on mortality. Not selected.
		Lin Y et al. (101)	Not powered on mortality. Not selected.
		Deiman BA et al. (102)	Not powered on mortality. Not selected.
		Wang Y et al. (103)	Not powered on mortality. Not selected.
		Ogawa H et al. (104)	Not powered on mortality. Not selected.
		Xiong R et al. A (105)	Not powered on mortality. Not selected.
		Xie X et al.(106)	Not powered on mortality. Not selected.
		Collet JP et al. (107)	Not powered on mortality. Not selected.
		Bonello-Palot N et al. (108)	Not powered on mortality. Not selected.
		Shuldiner AR et al. (109)	Not powered on mortality. Not selected.
		Frére C et al. (110)	Not powered on mortality. Not selected.
		Aleil B et al.(111)	Not powered on mortality. Not selected.
		Sibbing D et al. (112)	Not powered on mortality. Not selected.
		Brackbill ML et al. (113)	Not powered on mortality. Not selected.
		Giusti B et al. (114)	Not powered on mortality. Not selected.
		Umemura K et al. (115)	Not powered on mortality. Not selected.
		Frére C et al. (116)	Not powered on mortality. Not selected.

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>Fontana P et al. (117)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Giusti B et al. (118)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Brandt JT et al. (119)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No publication was selected therefore we will continue to the next step.
</td></tr>
<tr><td>4</td><td>Publications reporting predicted phenotype group: quality score 3</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Lee CR et al.(97)</td><td>Usable risk data: Yes (MACE)
Representative: Yes
Selected for extraction of tested groups.</td></tr>
<tr><td>Zhong Z et al. (98)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Wu Y et al. (99)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Cavallari LH et al. (100)</td><td>Usable risk data: Yes
Representative: Yes
Selected for extraction of tested groups.</td></tr>
<tr><td>Lin Y et al. (101)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Deiman BA et al. (102)</td><td>Usable risk data: No, only PM selected.
Representative: Yes
Not selected.</td></tr>
<tr><td>Wang Y et al. (103)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Ogawa H et al. (104)</td><td>Representative: No, Japanese patients.
Not selected.</td></tr>
<tr><td>Xiong R et al. A (105)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Xie X et al.(106)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Collet JP et al. (107)</td><td>Representative: No, only young and male patients selected.
Usable risk data: No
Not selected.</td></tr>
<tr><td>Bonello-Palot N et al. (108)</td><td>Usable risk data: No. Not genotype-guided.
Representative: Yes.
Not selected.</td></tr>
<tr><td>Shuldiner AR et al. (109)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Frére C et al. (110)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Aleil B et al.(111)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Sibbing D et al. (112)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Brackbill ML et al. (113)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Giusti B et al. (114)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Umemura K et al. (115)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Frére C et al. (116)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Fontana P et al. (117)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Giusti B et al. (118)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
<tr><td>Brandt JT et al. (119)</td><td>Usable risk data: No. Not genotype-guided.
Not selected.</td></tr>
</table>
Conclusion:
We have selected 2 publications (Lee CR et al.(97)and Cavallari LH et al. (100)) for the extraction of data for tested groups.
</td></tr>
<tr><td>5</td><td>Perform literature review in review of a</td><td>Not applicable</td></tr>
</table>

	usable study regarding the relevant DGI	

Absolute risk extraction non-actionables (UM and EM):

Sorich MJ et al.(79) was selected for extraction of non-actionables groups.

Sorich MJ et al. (79) is a meta-analysis assessing the association between CYP2C19 LoF allele carriage and major cardiovascular outcomes differs based on the ethnic population and the clopidogrel indication. Of the 23 studies in this meta-analysis, 15 studies were also included in the Mao 2014 meta-analysis, 9 in the Jang 2012 meta-analysis, 13 in the Holmes 2011 meta-analysis and 10 in the Liu 2011 meta-analysis. Five of the articles in the meta-analysis were also included separately in this risk analysis (Trenk 2008, Giusti 2009, Mega 2009, Sibbing 2009 and Simon 2009). Meta-analysis of 24 studies (23 publications) including a total of 36,076 patients using clopidogrel. 16 studies were performed in Caucasian populations (ntotal = 26,059), 8 in Asian populations (ntotal = 10,017). The meta-analysis only incorporated studies including n ≥ 500 patients.

Major adverse cardiovascular outcomes (death, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke): Sorich MH et al. (79) has combined the *CYP2C19* UM and EMs in one group, therefore we will also perform risk extraction for UM and EMs combined. Risk of major adverse cardiovascular outcomes was 0.091849866 (See Figure 2, white non-PCI + white PCI, sum of events/sum of patients = 449+1264/5152+13498) among non-actionable CYP2C19 UM and EMs. The risk of cardiovascular death in MACE is 0.34. Therefore, risk of death as a result of adverse cardiovascular events is 0.091849866 x 0.34 = 0.03146708 for non-actionable CYP2C19 UM and EMs. These are given a certainty score of 3.

Absolute risk extraction untested actionables (IM and PM):

Sorich MJ et al. (79) was selected for extraction of untested actionable groups.

Sorich MJ et al. (79) is a meta-analysis assessing the association between CYP2C19 LoF allele carriage and major cardiovascular outcomes differs based on the ethnic population and the clopidogrel indication. Of the 23 studies in this meta-analysis, 15 studies were also included in the Mao 2014 meta-analysis, 9 in the Jang 2012 meta-analysis, 13 in the Holmes 2011 meta-analysis and 10 in the Liu 2011 meta-analysis. Five of the articles in the meta-analysis were also included separately in this risk analysis (Trenk 2008, Giusti 2009, Mega 2009, Sibbing 2009 and Simon 2009). Meta-analysis of 24 studies (23 publications) including a total of 36,076 patients using clopidogrel. 16 studies were performed in Caucasian populations (n total = 26,059), 8 in Asian populations (n total = 10,017). The meta-analysis only incorporated studies including n ≥ 500 patients.

Major adverse cardiovascular outcomes (death, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke): Sorich MH et al. (79) has combined the CYP2C19 IMs and PMs in one group, therefore we will also perform risk extraction for IM and PMs combined. Risk of major adverse cardiovascular outcomes was 0.107436901 (See Figure 2, white non-PCI + white PCI, sum of events/sum of patients = 177+619/1891+5518) among untested actionable CYP2C19 IMs and PMs. The risk of cardiovascular death in MACE is 0.34 (120). Therefore, risk of death as a result of adverse cardiovascular events is 0.107436901 x 0.34 = 0.036807086 for untested actionable CYP2C19 IMs and PMs. These are given a certainty score of 3.

Absolute risk extraction tested actionables (IM and PM):

Lee CR et al.(97) and Cavallari LH et al. (100) were selected for the extraction of data for tested groups. Both studies have given CYP2C19 IMs and PMs alternative therapies with ticagrelor and prasugrel.

Lee CR et al.(97) assessed the feasibility, sustainability and clinical impact of using CYP2C19 genotype-guided dual antiplatelet therapy (DAPT) selection in practice remains unclear. This single-center observational study was conducted in 1,193 patients who underwent PCI and received DAPT following implementation of an algorithm that recommends CYP2C19 testing in high-risk patients and alternative DAPT (prasugrel or ticagrelor) in LOF allele carriers. The frequency of genotype testing and alternative DAPT selection were the primary implementation endpoints. Risk of major adverse cardiovascular or cerebrovascular (MACCE) and clinically significant bleeding events over 12 months were compared across genotype and DAPT groups. CYP2C19 genotype was obtained in 868 (72.8%) patients. Alternative DAPT was prescribed in 186 (70.7%) LOF allele carriers.

Cavallari LH et al. (100) is a multicenter pragmatic investigation assessed outcomes following clinical implementation of

CYP2C19 genotype–guided antiplatelet therapy after percutaneous coronary intervention (PCI). After clinical genotyping, each institution recommended alternative antiplatelet therapy (prasugrel, ticagrelor) in PCI patients with a loss-of-function allele. Major adverse cardiovascular events (defined as myocardial infarction, stroke, or death) within 12 months of PCI were compared between patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy. Risk was also compared between patients without a loss-of-function allele and loss-of-function allele carriers prescribed alternative therapy. Among 1,815 patients, 572 (31.5%) had a loss-of-function allele. The risk for major adverse cardiovascular events was significantly higher in patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy(23.4 vs. 8.7 per 100 patient-years; adjusted hazard ratio: 2.26; 95% confidence interval: 1.18 to 4.32; p = 0.013). Similar results were observed among 1,210

patients with acute coronary syndromes at the time of PCI (adjusted hazard ratio:2.87; 95% confidence interval: 1.35 to 6.09; p = 0.013).

Lee CR et al.(97) and Cavallari LH et al. have combined the CYP2C19 IM and PMs in one group, therefore we will also perform risk extraction for IM and PMs combined.

Lee CR et al.(97): Risk of major cardiovascular events was 0.053763441 (See Figure 3A, LOF-alt, n events/n patients (extracted from Fig 1A) =10/186) among actionable CYP2C19 IM and PMs.

Cavallari LH et al. (100): Risk of major cardiovascular events was 0.080924855 (See Table 3, LOF-alternative, n events/n patients =28/346) among actionable CYP2C19 IM and PMs.

	Lee CR et al.(97)	Cavallari LH et al. (100)	Total
Number of MACE	10	28	38
Number of patients CYP2C19 IM or PM who received alternative P2Y12 inhibitor	186	346	532
Overall absolute risk	-	-	0.071428571

The risk of cardiovascular death in MACE is 0.34 (120). Therefore, risk of death as a result of adverse cardiovascular events is 0.071428571x 0.34 = 0.024470899 for tested actionable CYP2C19 IMs and PMs. These are given a certainty score of 1.

Conclusion of selected publications and absolute risks extracted:

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Clopidogrel	CYP2C19 EM	No	0.031467084	(79)	3	0.031467084	(79)	3
Clopidogrel	CYP2C19 IM	Yes	0.036807086	(79)	3	0.024470899	(97, 100)	1
Clopidogrel	CYP2C19 PM	Yes	0.036807086	(79)	3	0.024470899	(97, 100)	1
Clopidogrel	CYP2C19 UM	no	0.031467084	(79)	3	0.031467084	(79)	3

Ref: Reference; CS: certainty score

UGT1A1-IRINOTECAN

Publication selection

Risk analysis: https://kennisbank.knmp.nl/files/farmacogenetica/1691-1692.PDF

<table>
<tr><td></td><td>Steps performed systematically to select suitable publication(s) form which extraction is performed</td><td>Publication(s) selection</td></tr>
<tr><td>1</td><td>Publications reporting predicted phenotype group: quality score 4, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Chen X et al. (121)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Liu XH et al. (122)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Han FF et al. (123)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Chen YJ et al. (124)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Liu X et al.(125)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Hu ZY et al. (126)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Hu ZY et al. (127)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Hoskins JM et al. (128)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Dias MM et al. (129)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Liu X et al. (130)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Dias MM et al.(131)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Denlinger CS et al.(132)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No publication was selected therefore we will continue to the next step.</td></tr>
<tr><td>2</td><td>Publications reporting predicted phenotype group: quality score 4</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Chen X et al. (121)</td><td>Usable risk data: Yes
Representative: No, Asian patients.
Not selected.</td></tr>
<tr><td>Liu XH et al. (122)</td><td>Usable risk data: Yes
Representative: No, less than 50% of the studies performed in Caucasian population.
Not selected.</td></tr>
<tr><td>Han FF et al. (123)</td><td>Usable risk data: No (only ORs)
Representative: No, Asian patients.
Not selected.</td></tr>
<tr><td>Chen YJ et al. (124)</td><td>Usable risk data: No
Representative: No, Asian patients.
Not selected.</td></tr>
<tr><td>Liu X et al.(125)</td><td>Usable risk data: Yes
Representative: Yes
Selected for extraction of untested groups.</td></tr>
<tr><td>Hu ZY et al. (126)</td><td>Usable risk data: No (only ORs)
Representative: Yes
Not selected.</td></tr>
<tr><td>Hu ZY et al. (127)</td><td>Usable risk data: Yes
Representative: Yes
Not selected. Another meta-analysis is more recent.</td></tr>
<tr><td>Hoskins JM et al. (128)</td><td>Usable risk data: No, only looks at *28/*28 vs. *1/*1 + *28/*1
Representative: Yes
Not selected.</td></tr>
<tr><td>Dias MM et al. (129)</td><td>Usable risk data: No
Not selected.</td></tr>
<tr><td>Liu X et al. (130)</td><td>Usable risk data: No
Representative: Yes
Not selected.</td></tr>
<tr><td>Dias MM et al.(131)</td><td>Usable risk data: No
Not selected.</td></tr>
<tr><td>Denlinger CS et al.(132)</td><td>Usable risk data: No
Not selected.</td></tr>
</table>
Conclusion:</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Liu X et al.(125) was selected for extraction of untested and non-actionable groups. Therefore we will continue with the next step to obtain the data for the tested groups.</td></tr>
<tr><td>3</td><td>Publications reporting predicted phenotype group: quality score 3, powered on mortality</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Lu CY et al. (133)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Goetz MP et al. (134)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kweekel DM et al. (135)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Liu CY et al. (136)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Lankisch TO et al. (137)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Minami H et al. (138)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Stewart CF et al. (139)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Côté JF et al. (140)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Ramchandani RP et al..(141)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Zárate Romero R et al. (142)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>de Jong FA et al. (143)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Toffoli G et al. (144)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Han JY et al.(145)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>McLeod HL et al. (146)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Massacesi C et al. (147)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Wright MA et al. (148)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kweekel DM etal.</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Soepenberg O et al. (149)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Zhou Q et al. (150)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Carlini LE et al. (151)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Kitagawa C et al. (152)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Marcuello E et al. (153)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Rouits E et al.(154)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Paoluzzi L et al. (155)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Sai K et al. (156)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Innocenti F et al. (157)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Font A et al. (158)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Mathijssen RH et al. (159)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Iyer L et al. (160)</td><td>Not powered on mortality. Not selected.</td></tr>
<tr><td>Ando Y et al. (161)</td><td>Not powered on mortality. Not selected.</td></tr>
</table>
Conclusion:
No publication was selected therefore we will continue to the next step.
</td></tr>
<tr><td>4</td><td>Publications reporting predicted phenotype group: quality score 3</td><td>
<table>
<tr><th>Study</th><th>Conclusion</th></tr>
<tr><td>Lu CY et al. (133)</td><td>Representative: No, Taiwanese patients.
Not selected.</td></tr>
<tr><td>Goetz MP et al. (134)</td><td>Representative: Yes
Usable risk data: No.
Not selected.</td></tr>
<tr><td>Kweekel DM et al. (135)</td><td>Representative: Yes
Usable risk data: No, not genotype-guided.
Not selected.</td></tr>
<tr><td>Liu CY et al. (136)</td><td>Representative: No, Chinese patients.
Not selected.</td></tr>
<tr><td>Lankisch TO et al. (137)</td><td>Representative: Yes
Usable risk data: No, not genotype-guided.
Not selected.</td></tr>
<tr><td>Minami H et al. (138)</td><td>Representative: No, Japanese patients.
Not selected.</td></tr>
<tr><td>Stewart CF et al. (139)</td><td>Representative: No, pediatric population.
Usable risk data: No, not genotype-guided
Not selected.</td></tr>
<tr><td>Côté JF et al. (140)</td><td>Usable risk data: No, not genotype-guided
Not selected.</td></tr>
<tr><td>Ramchandani RP et al..(141)</td><td>Usable risk data: No, not genotype-guided
Not selected.</td></tr>
<tr><td>Zárate Romero R et al. (142)</td><td>Usable risk data: No, not genotype-guided
Not selected.</td></tr>
</table>
</td></tr>
</table>

		de Jong FA et al. (143)	Usable risk data: No, not genotype-guided Not selected.
		Toffoli G et al. (144)	Usable risk data: No, not genotype-guided Not selected.
		Han JY et al.(145)	Usable risk data: No, not genotype-guided Not selected.
		McLeod HL et al. (146)	Usable risk data: No, not genotype-guided Not selected.
		Massacesi C et al. (147)	Usable risk data: No, not genotype-guided Not selected.
		Wright MA et al. (148)	Usable risk data: No, not genotype-guided Not selected.
		Kweekel DM etal.	Usable risk data: No, not genotype-guided Not selected.
		Soepenberg O et al. (149)	Usable risk data: No, not genotype-guided Not selected.
		Zhou Q et al. (150)	Usable risk data: No, not genotype-guided Not selected.
		Carlini LE et al. (151)	Usable risk data: No, not genotype-guided Not selected.
		Kitagawa C et al. (152)	Usable risk data: No, not genotype-guided Not selected.
		Marcuello E et al. (153)	Usable risk data: No, not genotype-guided Not selected.
		Rouits E et al.(154)	Usable risk data: No, not genotype-guided Not selected.
		Paoluzzi L et al. (155)	Usable risk data: No, not genotype-guided Not selected.
		Sai K et al. (156)	Usable risk data: No, not genotype-guided Not selected.
		Innocenti F et al. (157)	Usable risk data: No, not genotype-guided Not selected.
		Font A et al. (158)	Usable risk data: No, not genotype-guided Not selected.
		Mathijssen RH et al. (159)	Usable risk data: No, not genotype-guided Not selected.
		Iyer L et al. (160)	Usable risk data: No, not genotype-guided Not selected.
		Ando Y et al. (161)	Usable risk data: No, not genotype-guided Not selected.
		Conclusion: No publication was selected therefore we will continue to the next step.	
5	Perform literature review in review of a usable study regarding the relevant DGI	**Search strategy pubmed**	**Date literature search**
		Irinotecan[Title] AND (UGT1A1[Title] OR Pharmacogenetic[Title] OR Pharmacogenetics [Title] OR genotype[Title] OR genotypes[Title] OR polymorphism[Title] OR polymorphisms[Title])	18-12-2019
		Conclusion: We found no intervention studies through our own literature search. Therefore, we estimated the absolute risk on death to be equal to that of non-actionables. These are given a certainty score of 0.	

Absolute risk extraction non-actionables (*1/*1, *1/*28 and IM):

Liu X et al.(125)is a meta-analysis of 16 studies including a total of 2,328 mainly Caucasian patients with colorectal cancer. The outcome measure was grade 3-4 toxicity.

Neutropenia:

Risk of grade 3 or higher neutropenia was 0.1121 (See Figure 2, b, high IRI, sum of events/sum of patients = 72/642) among non-actionable *1/*1. Risk of drug-related death as a result of myelosuppression is 0.00949 (section treatment related deaths:

1.3% died of treatment related effects, of which 73% was associated with myelosuppression) (162). Therefore, risk of death as a result of grade 3 neutropenia is 0.1121 x .,00949 = 0.001064299 for non-actionable *1/*1. These are given a certainty score of 3.

Risk of grade 3 or higher neutropenia was 0.1865 (See Figure 3, b, high IRI, sum of events/sum of patients = 102/547) among non-actionable *1/*28 and IMs. Risk of death as a result of myelosupression is 0.00949 (section treatment related deaths: 1.3% died of treatment related effects, of which 73% was associated with myelosuppression) (162). Therefore, risk of death as a result of grade 3 neutropenia is 0.1865 x 0.00949 = 0.001769616 for non-actionable *1/*28 and IM. These are given a certainty score of 3.

Diarrhoea:

Risk of grade 3 or higher diarrhoea was 0.1109 (See Figure 4, b, high IRI, sum of events/sum of patients = 73/658) among non-actionable *1/*1. Risk of drug-related death as a result of diarrhoea is 0.001363473 (section treatment related deaths sum of patients death of diarrhoea/total patients = 19/13935) . Therefore, risk of death as a result of grade 3 diarrhoea is 0.1109 x 0.0013 = 0.000151267 for non-actionable *1/*1. These are given a certainty score of 3.

Risk of grade 3 or higher diarrhoea was 0.1473 (See Figure 5, b, high IRI, sum of events/sum of patients = 80/543) among non-actionable *1/*28 and IM. Risk of drug-related death as a result of diarrhoea is 0.001363473 (section treatment related deaths sum of patients death of diarrhoea/total patients = 19/13935) (162). Therefore, risk of death as a result of grade 3 diarrhoea is 0.1473 x 0.0013 = 0.00020088 for non-actionable *1/*28 and IM. These are given a certainty score of 3.

Absolute risk extraction untested actionables (*28/*28 and PM):

Liu X et al.(125). is a meta-analysis of 16 studies including a total of 2,328 mainly Caucasian patients with colorectal cancer. The outcome measure was grade 3-4 toxicity.

Neutropenia:

Risk of grade 3 or higher neutropenia was 0.3525 (See Figure 2, b, high IRI, sum of events/sum of patients = 43/122) among untested *28/*28 and PM. Risk of drug-related death as a result of myelosupression is 0.00949 (section treatment related deaths: 1.3% died of treatment related effects, of which 73% was associated with myelosuppression) (162). Therefore, risk of death as a result of grade 3 neutropenia is 0.3525 x 0.00949 = 0.003344836 for untested *28/*28 and PM. These are given a certainty score of 3.

Diarrhoea:

Risk of grade 3 or higher diarrhoea was 0.2155 (See Figure 4, b, high IRI, sum of events/sum of patients = 25/116) among untested *28/*28 and PM. Risk of drug-related death as a result of grade 3 diarrhoea is approximately 0.001363473 (section treatment related deaths sum of patients death of diarrhoea/total patients = 19/13935) (162). Therefore, risk of death as a result of grade 3 diarrhoea is 0.2155 x 0.001 = 0.000293852 for untested *28/*28 and PM. These are given a certainty score of 3.

Absolute risk extraction tested actionables (*28/*28 and PM):

Since no intervention studies were identified, we estimate the risk of death for tested-actionables to equal the risk of death of non-actionables (*1/*1). In this case it is given a certainty score of 0 (estimation).

Conclusion of selected publications and absolute risks extracted (death as a result of neutropenia):

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Irinotecan	UGT1A1 *1/*1	no	0.001064299	(125)	3	0.001064299	(125)	3
Irinotecan	UGT1A1 *1/*28	no	0.001769616	(125)	3	0.001769616	(125)	3
Irinotecan	UGT1A1 *28/*28	yes	0.003344836	(125)	3	0.001064299	-	0
Irinotecan	UGT1A1 IM	no	0.001769616	(125)	3	0.001769616	(125)	3
Irinotecan	UGT1A1 PM	yes	0.003344836	(125)	3	0.001064299	-	0

Ref: Reference; CS: certainty score

Conclusion of selected publications and absolute risks extracted (death as a result of diarrhoea):

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Irinotecan	UGT1A1 *1/*1	no	0.000151267	(125)	3	0.000151267	(125)	3
Irinotecan	UGT1A1 *1/*28	no	0.00020088	(125)	3	0.00020088	(125)	3
Irinotecan	UGT1A1 *28/*28	yes	0.000293852	(125)	3	0.000151267	-	0
Irinotecan	UGT1A1 IM	no	0.00020088	(125)	3	0.00020088	(125)	3
Irinotecan	UGT1A1 PM	yes	0.000293852	(125)	3	0.000151267	-	0

Ref: Reference; CS: certainty score

Conclusion of selected publications and absolute risks extracted (sum absolute risk of death due to neutropenia and absolute risk of death due to diarrhoea):

		Actionability	Untested	Ref	CS	Tested	Ref	CS
Irinotecan	UGT1A1 *1/*1	no	0.001215566	(125)	3	0.001215566	(125)	3
Irinotecan	UGT1A1 *1/*28	no	0.001970496	(125)	3	0.001970496	(125)	3
Irinotecan	UGT1A1 *28/*28	yes	0.003638688	(125)	3	0.001215566	-	0
Irinotecan	UGT1A1 IM	no	0.001970496	(125)	3	0.001970496	(125)	3
Irinotecan	UGT1A1 PM	yes	0.003638688	(125)	3	0.001215566	-	0

Ref: Reference; CS: certainty score

Assessment of risk of drug-related death following an intermediary outcome associated with the gene-drug interaction

Interaction	Intermediary outcome associated with drug-gene interaction	AR of drug-related death as a result of the intermediary outcome	Description of reference	Ref
TPMT-azathioprine *TPMT*-mercaptopurine *TPMT*-thiopurine	Grade≥3 leucopenia	1%	A review of AZA/MP-induced myelotoxicity in inflammatory bowel disease (IBD) patients. In total, 66 studies (8,302 patients) were included. The cumulative incidence of AZA/MP-induced myelotoxicity was 7% (95% confidence interval [CI] 6-8%). The risk of death among patients who developed myelotoxicity was 0.94% (95% CI 0.32-2.70%). The author concludes with: the risk of death among IBD patients who develop myelotoxicity is approximately 1%.	(37)
DPYD-capecitabine *DPYD*-fluorouracil	Grade≥3 fluoropyrimidine-induced toxicity	0.75%	This article reviews the pharmacology and efficacy of capecitabine with a special emphasis on its safety. Among seven studies of 290 patients older than 55 years with breast cancer, three treatment-related deaths were observed at the dose of 1255 mg/m2 twice daily on an intermittent schedule (2 weeks on/1 week off).	(75)
CYP2C19-clopidogrel	MACE (death/cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke)*	34%	We calculated the risk of cardiovascular death within MACE from this publication. When multiplied with RR of MACE we are left with risk cardiovascular death. A Cochrane review was used for extraction of this risk. This review regarded clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events. It includes data from 15 trials with 33,970 people. The risk of cardiovascular death is 37/108 = 0.34 within a median follow-up of 12 months (averages from column Risk with clopidogrel plus aspirin in Summary of findings on page 4 were used).	(120)
UGT1A1-irinotecan	Grade≥3 neutropenia Grade≥3 diarrhea	0.9% 0.1%	A post marketing survey of irinotecan into severe adverse effects and treatment-related deaths. The number of deaths from severe adverse drug reactions	(162)

	whose causal relationship with irinotecan could not be ruled out was 176 (1.3%) of the 13 935 patients. Of the 176 TRDs, 103 (59%) were caused by myelosuppression, 19 (11%) by myelosuppression accompanied by diarrhea, 6 (3%) by myelosuppression with ileus, 20 (11%) by interstitial lung disease, 8 (5%) by renal failure, and 1 by diarrhea. Of all TRDs, 73% were associated with myelosuppression, or concurrent incidence of myelosuppression, ileus and diarrhea. Therefore, risk of death as a result of treatment-related myelosuppression is 1.3% * 73% = 0.9% and risk of death as a result of treatment-related diarrhea is 19/13935 = 0.1%.

References Appendix

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Appendix 4 Costs used in the decision analytic model

Input	Regimen	Dose form	Cost	Source
PGx test for *TPMT*	-	-	€ 132 per test	Leiden University Medical Center prices based on the Dutch Healthcare Authority (NZa) in 2018
PGx test for *DPYD*	-	-	€ 132 per test	Leiden University Medical Center prices based on the Dutch Healthcare Authority (NZa) in 2018
PGx test for *CYP2C19*	-	-	€ 132 per test	Leiden University Medical Center prices based on the Dutch Healthcare Authority (NZa) in 2018
PGx test for *UGT1A1*	-	-	€ 66 per test	Leiden University Medical Center prices based on the Dutch Healthcare Authority (NZa) in 2018
Pharmacist time	-	-	€12.11 per 18 minutes	Time: Reference (1) Salary: Clinical Pharmacists as standardized in Dutch Academic Hospitals in 2019 (2)
Physician time	-	-	€4.28 per 6 minutes	Time: Reference (1) Salary: Medical Specialists as standardized in Dutch Academic Hospitals in 2019 (2)
Azathioprine 100% (EM)	1dd 2mg/kg	2x tablet 75mg	€ 0.34 per tablet	Medicijnkosten.nl (3)
Azathioprine 50% (IM)	1dd 1mg/kg	2 x tablet 75mg	€ 0.34 per tablet	Medicijnkosten.nl (3)
Azathioprine 10% (PM)	1dd 0.5mg/kg	1 x tablet 50mg	€ 0.19 per tablet	Medicijnkosten.nl (3)
Capecitabine 100% (GAS 2)	2dd 1250mg/m^2 for 2 weeks. 1 week rest. for 6 months	4 x tablet 500mg	€ 1.24 per tablet	Medicijnkosten.nl (3)
Capecitabine 50% (GAS 1.5, 1)	2dd 625mg/m^2 for 2 weeks. 1 week rest. for 6 months	2x tablet 500mg	€ 1.24 per tablet	Medicijnkosten.nl (3)
Capecitabine alternative (GAS 0.5, 0)	Assumed same cost as capecitabine 100%			
Clopidogrel (EM, UM)	1dd75mg	1x tablet 75mg	€ 0.04 per tablet	Medicijnkosten.nl (3)
Clopidogrel 200% (IM)	1dd150mg	2x tablet 75mg	€ 0.04 per tablet	Medicijnkosten.nl (3)
Clopidogrel alternative 1 (PM, ACS -25%)	ticagrelor: 2dd90mg	2 x tablet 90mg	€ 1.24 per tablet	Medicijnkosten.nl (3)
Clopidogrel alternative 2 (PM, ACS - 25%)	prasugrel: 1dd10mg	1 x tablet 10mg	€ 1.63 per tablet	Medicijnkosten.nl (3)
Clopidogrel alternative 3 (PM, TIA -50%)	dipyridamol: 2dd200mg	4 x tablet 200mg	€ 0.25 per tablet	Medicijnkosten.nl (3)

Clopidogrel alternative overall	Assumed 50% ACS indication (prasugrel and ticagrelor) and 50% TIA (dipyridamol)			
5-FU 100% (GAS 2)	400mg/m^2 2x per month for 6 months	1 x vial 50mg/mL 20mL	€ 6.81 per dose	Medicijnkosten.nl (3)
5-FU 50% (GAS 1.5, 1)	200mg/m^2 2x per month for 6 months	1 x vial 50mg/mL 10mL	€ 3.40 per dose	Medicijnkosten.nl (3)
5-FU alternative (GAS 0.5, 0)	Assumed same cost as 5-FU 100%			
Irinotecan 100% (EM)	350mg/m^2 every 3 weeks	1 x vial 20mg/mL 25mL and 1 x vial 20mg/mL 5 mL	€ 856.25 per dose	Medicijnkosten.nl (3)
Irinotecan 70% (*28/*28, PM)	245mg/m^2 every 3 weeks	1 x vial 20mg/ml 25mL	€ 712.74 per dose	Medicijnkosten.nl (3)
Mercaptopurine 100%	1dd 1.5mg/kg	2 x tablet 50mg	€ 2.68 per tablet	Medicijnkosten.nl (3)
Mercaptopurine 50% (IM)	1dd 0.75mg/kg	1 x tablet 50mg	€ 2.68 per tablet	Medicijnkosten.nl (3)
Mercaptopurine 10% (PM)	1dd 0.15mg/kg	15mg/mL 1mL vial	€ 16.35 per dose	Medicijnkosten.nl (3)
Tioguanine 100% (EM)	1dd 0.3mg/kg	1 x capsule 21mg	€ 2.98 per capsule	Medicijnkosten.nl (3)
Tioguanine 75% (IM)	1dd 0.225mg/kg	1 x capsule 16mg	€ 2.75 per capsule	Medicijnkosten.nl (3)
Tioguanine 6% (PM)	1dd 0.018mg/kg	1 x capsule 10mg	€ 2.49 per capsule	Medicijnkosten.nl (3)

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