Supplementary Material

Supplementary Table 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%)
Supplementary Table 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 |

\textsuperscript{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]. \textsuperscript{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 good performed meta-analyzes.
plasma level, AUC, half-life, etc.) or poor performed meta-analyses (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 publications are 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:**

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
**Supplementary Table 3** Systematic selection of literature and extraction of absolute risk of gene-drug-related death

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1.1 TPMT-AZATHIPURINE/MERCAPTOPURINE

1.1.1 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.

| Steps performed systematically to select suitable publication(s) form which extraction is performed | Publication(s) selection |
|----------------------------------------------------------------------------------------------------|--------------------------|
| Publications reporting predicted phenotype group: quality score 4, powered on mortality             |                          |
| Study                                                                                              | Conclusion               |
| Relling MJ et al.(1)                                                                                | Not powered on mortality. Not selected. |
| Lui C et al.(2)                                                                                     | Not powered on mortality. Not selected. |
| Booth RA et al.(3)                                                                                  | Not powered on mortality. Not selected. |
| Zelinkova Z et al.(4)                                                                               | Not powered on mortality. Not selected. |
| Fabre MA et al. (5)                                                                                 | Not powered on mortality. Not selected. |
| Pandya B et al.(6)                                                                                 | Not powered on mortality. Not selected. |
| Stanulla M et al.(7)                                                                               | Not powered on mortality. Not selected. |

Conclusion: No literature was selected therefore we will continue to the next step.

| 2 Publications reporting predicted | Study       | Conclusion |
|------------------------------------|-------------|------------|

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| Publication | Usable risk data | Representative | Conclusion |
|-------------|------------------|----------------|------------|
| Relling MJ et al. (1) | Yes | No | Usable risk data: Yes Representative: No, indication in this study is ALL patients. Not selected. |
| Lui C et al. (2) | | | Representative: No, indication in this study is ALL patients. Not selected. |
| Booth RA et al. (3) | Yes | Yes | Selected for extraction of untested and non-actionable groups. |
| Zelinkova Z et al. (4) | Yes | Yes | Representative: Yes Usable risk data: Yes Not selected. (Data is included in included meta-analysis by Booth et al.) |
| Fabre MA et al. (5) | | | Representative: No, indication in kidney transplantation patients. Not selected. |
| Pandya B et al. (6) | | | Representative: No, indication in kidney transplantation patients. Not selected. |
| Stanulla M et al. (7) | | | Representative: No, indication in this study is ALL patients. Not selected. |

**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.

| Study | Conclusion |
|-------|------------|
| Fan X et al. (8) | Not powered on mortality. Not selected. |
| Choi R et al. (9) | Not powered on mortality. Not selected. |
| Eriksen P et al. (10) | Not powered on mortality. Not selected. |
| Coenen MJ et al. (11) | Not powered on mortality. Not selected. |
| Lennard L et al. (12) | Not powered on mortality. Not selected. |
| Author(s)                  | Note                                                                 |
|---------------------------|----------------------------------------------------------------------|
| Lennard L et al. (13)     | Not powered on mortality. Not selected.                               |
| Kim MJ et al. (14)        | Not powered on mortality. Not selected.                               |
| Leninsen M et al. (15)    | Not powered on mortality. Not selected.                               |
| 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.                               |
| Sheffield 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.                               |
| Study                      | Included in input data                                                                 |
|----------------------------|-----------------------------------------------------------------------------------------|
| 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                                                                   |

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| Reference                          | Representative                  | Usable risk data                              | Selected |
|-----------------------------------|---------------------------------|-----------------------------------------------|----------|
| Dong XW et al. (18)               | Not selected                   |                                               |          |
| Hildorf U et al. (19)             | Representative: No, less <50% of studies western. Not selected. |                                               |          |
| Sheffield L et al. (20)           | Representative: No, autoimmune hepatitis patients. Not selected. |                                               |          |
| Ansari A et al. (21)              | Representative: Yes             | Usable risk data: No, not genotype-guided.    |          |
| Gardiner S et al. (22)            | Representative: Yes             | Usable risk data: No, not genotype-guided.    |          |
| 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.    |          |
| Ansari A et al. (28)              | Representative: Yes             | Usable risk data: No, not genotype-guided.    |          |
| Reference                  | Representative | Usable risk data | Not selected |
|----------------------------|----------------|------------------|--------------|
| Langley P et al. (29)      | No, autoimmune hepatitis patients. |                  |              |
| Regueiro M et al. (30)     | Yes            | No, not genotype-guided. |              |
| Campbell S et al. (31)     | Yes            | No, not genotype-guided. |              |
| Colombel JF et al. (32)    | Yes            | No, not genotype-guided. |              |
| Black AJ et al. (33)       | No, rheumatic patients. |                  |              |
| Higgs JE et al. (34)       | No, not specific for IBD. |                  |              |
| Evans et al. (35)          | No, ALL patients. |                  |              |
| McLeod HL et al. (36)      | No, ALL patients. |                  |              |

Conclusion: Coenen MJ et al. (11) was selected for extraction for tested-actionable groups.

### 1.1.2 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.

1.1.3 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.

1.1.4 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 < 3.0x10^9/L or platelet count < 100x10^9/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.
1.1.5 Conclusion of selected publications and absolute risks extracted:

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

Ref: Reference; CS: Certainty score
1.2  *TPMT*-TI OG UANINE

1.2.1 Publication selection

Risk analysis: [https://kennisbank.knmp.nl/files/farmacogenetica/1907-1908.PDF](https://kennisbank.knmp.nl/files/farmacogenetica/1907-1908.PDF)

| Steps performed systematically to select suitable publication(s) form which extraction is performed | Publication(s) selection |
|---|---|
| 1 Publications reporting predicted phenotype group: quality score 4, powered on mortality | 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. |

| 2 Publications reporting predicted phenotype group: quality score 4 | 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. |

| 3 Publications reporting predicted phenotype group: quality score 3, powered on mortality | Study | Conclusion |
|---|---|---|
| Lennard L et al. (13) | Not powered for mortality |
| Wray L et al. (38) | Not powered for mortality |
| Lennard L et al. (39) | Not powered for mortality |
| Teml A et al. (40) | Not powered for mortality |
| Herrlinger KR et al.(41) | Not powered for mortality |

Conclusion: No literature was selected therefore we will continue to the next step.

| 4 Publications reporting predicted phenotype group: quality score 3 | Study | Conclusion |
|---|---|---|
| Lennard L et al. (13) | Usable risk data: No |
| Wray L et al. (38) | Usable risk data: No Patients are children with ALL. |
| Lennard L et al. (39) | Usable risk data: No Patients are children with ALL. |
| Teml A et al. (40) | Usable risk data: No. Very small study population. |
Herrlinger KR et al.(41)  Usable risk data: No. Very small study population.

Conclusion:
No literature was selected therefore we will continue to the next step.

Perform literature review in review of a usable study regarding the relevant DGI

**Search strategy pubmed**

(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])

Date literature search

02-12-2019

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.

### 1.2.2 Conclusion of selected publications and absolute risks extracted:

| DGI       | Actionability | Untested | Ref | CS  | Tested | Ref | CS  |
|-----------|---------------|----------|-----|-----|--------|-----|-----|
| Thioguanine TPMT EM | no            | 0.002095738 | (3)  | 0.002095738 | (3)  | 0   |
| Thioguanine TPMT IM | yes           | 0.003904762 | (3)  | 0.00025641 | (11) | 0   |
| Thioguanine TPMT PM | yes           | 0.01     | (3)  | 0.00025641 | (11) | 0   |
### 1.3 DPYD-CAPECITABINE/5-FU

#### 1.3.1 Publication selection

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

| Steps performed systematically to select suitable publication(s) form which extraction is performed | Publication(s) selection |
|---|---|
| **1** Publications reporting predicted phenotype group: quality score 4, powered on mortality | **Study** | **Conclusion** |
| Deenen MJ et al. (42) | Not powered on mortality. Not selected. |
| Meulendijks D et al. (43) | Not powered on mortality. Not selected. |
| Meulendijks D et al.(44) | Not powered on mortality. Not selected. |
| Rosmarin D et al.(45) | Not powered on mortality. Not selected. |
| Terrazzino S et al. (46) | Not powered on mortality. Not selected. |
| Vulsteke C et al. (47) | Not powered on mortality. Not selected. |

**Conclusion:**
No publication was selected therefore we will continue to the next step.

| **2** Publications reporting predicted phenotype group: quality score 4 | **Study** | **Conclusion** |
|---|---|---|
| Deenen MJ et al. (42) | 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)) |
| Meulendijks D et al. (43) | Usable risk data: Yes Representative: No. Study only in small population for specific alleles. Not selected. |
| Study | Usable risk data: Yes | Representative: Yes | Selected for extraction of untested groups. |
|-------|-----------------------|----------------------|---------------------------------------------|
| Meulendijks D et al. (44) | | | |
| Rosmarin D et al. (45) | Usable risk data: No | Representative: Yes | Not selected. |
| Terrazzino S et al. (46) | Usable risk data: Yes | Representative: Yes | Not selected. Another meta-analysis is more recent. |
| Vulsteke C et al. (47) | Usable risk data: Yes. | Representative: Yes | Not selected. Another meta-analysis is more recent. |

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.

| Study | Conclusion |
|-------|------------|
| Kleinjan JP et al. (48) | Not powered on mortality. Not selected. |
| Henricks LM et al. (49) | Not powered on mortality. Not selected. |
| Lunenburg CATC et al. (50) | Not powered on mortality. Not selected. |
| Henricks LM et al. (51) | Not powered on mortality. Not selected. |
| Madi A et al. (52) | Not powered on mortality. Not selected. |
| Lunenburg CA et al. (53) | Not powered on mortality. Not selected. |
| Lee AM et al. (54) | Not powered on mortality. Not selected. |
| Deenen MJ et al. (55) | Not powered on mortality. Not selected. |
| Authors                        | Status                        |
|-------------------------------|-------------------------------|
| Lee AM et al. (56)            | Not powered on mortality. Not selected. |
| van Kuilenburg AB et al. (57) | Not powered on mortality. Not selected. |
| Kristensen MH et al. (58)     | Not powered on mortality. Not selected. |
| Gross E et al. (59)           | Not powered on mortality. Not selected. |
| Capitain O et al. (60)        | Not powered on mortality. Not selected. |
| 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.

| 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? |
| Study Authors          | Usable Risk Data                                      | Representative                        | Selection Status |
|-----------------------|-------------------------------------------------------|---------------------------------------|------------------|
| Lee AM et al. (56)    | Usable risk data: no risk for tested actionables      |                                       | Not selected.    |
|                       | reported.                                             |                                       |                  |
|                       | Not selected.                                         |                                       |                  |
| van Kuilenburg AB et  | Representative: Yes, Dutch population.                |                                       | Not selected.    |
| al. (57)              | Usable risk data: No, not genotype-guided.            |                                       |                  |
| Kristensen MH et      | Usable risk data: no, not genotype-guided.            |                                       | Not selected.    |
| al. (58)              |                                                       |                                       |                  |
| 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  | Usable risk data: No, not genotype-guided.            |                                       | Not selected.    |
| al. (61)              |                                                       |                                       |                  |
| Schwab M et al. (62)  | Usable risk data: No, not genotype-guided.            |                                       | Not selected.    |
| Mercier C et al.      | Representative: Yes                                   |                                       | Not selected.    |
|                       | Usable risk data: No                                  |                                       |                  |
|                       | Not selected.                                         |                                       |                  |
| Jatoi A et al. (63)   | Representative: Yes                                   |                                       | Not selected.    |
|                       | Usable risk data: No                                  |                                       |                  |
|                       | Not selected.                                         |                                       |                  |
| Magné N et al. (64)   | Representative: Yes                                   |                                       | Not selected.    |
|                       | Usable risk data: No                                  |                                       |                  |
|                       | Not selected.                                         |                                       |                  |
| Boisdron-Celle M et   | Usable risk data: No, not genotype-guided.            | Representative: Yes                   | Not selected.    |
| al. (65)              |                                                       |                                       |                  |
|                       |                                                        |                                       |                  |
| Cho HJ et al. (66)    | Representative: No. Study is done in Korean           |                                       | Not selected.    |
|                       | population.                                           |                                       |                  |
|                       |                                                       |                                       |                  |
| Study Reference                  | Representative | Usable risk data: | Not selected. |
|--------------------------------|----------------|------------------|---------------|
| Salgado J et al. (67)           | Yes            | No, not genotype-guided. Not selected. |
| Morel A et al. (68)             | Yes            | No, not genotype-guided. Not selected. |
| Largillier R et al. (69)        | Yes            | No, not genotype-guided. Not selected. |
| Salgueiro N et al. (70)         | Yes            | No, not genotype-guided. Not selected. |
| Van Kuilenburg AB et al. (71)   | Yes            | No, not genotype-guided. Not selected. |
| Raida M et al. (72)             | Yes            | No, not genotype-guided. Not selected. |
| Yamaguchi K et al. (73)         | No. Study is done in Japanese population. Not selected. |
| van Kuilenburg AB et al. (74)   | Yes            | 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 |

**1.3.2 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.

1.3.3 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 GAS 1.0. 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 \([\text{risk of death GAS } 1.5 + \text{delta risk}] = 0.005176056 + 0.0018 = 0.0070\). 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 \([\text{risk of death GAS } 0.5 + \text{delta risk}] = 0.0070 + 0.0018 = 0.0088\). These are given a certainty score of 0.

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

Kleinjan JP et al. \(48\), Henricks LM et al. \(49\), 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).

Henriks 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 |
|-------------------------|------------------------|--------------------------|------------------------|----------------------|-------|

25
*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 patients GAS 0.5 | Not reported            | Not reported              | Not reported             | Not reported        | Not applicable |
| 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 applicable |
| Number of events       | 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.

1.3.5 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 | -  |
| Capecitabine/5-FU        | DPYD GAS 0.5  | yes      | 0.0070 | -  | 0      | 0.0012 | -  |
| Capecitabine/5-FU        | DPYD GAS 1.0  | yes      | 0.005176056 | (44) | 3 | 0.0013 | (48) | (49, 50) | (51, 55) |
| Capecitabine/5-FU        | DPYD GAS 1.5  | yes      | 0.003377863 | (44) | 3 | 0.0010 | (48) | (50) | (51) |
| Capecitabine/5-FU        | DPYD GAS 2    | no       | 0.002430066 | (44) | 3 | 0.002430066 | (44) | 3 |

Ref: Reference; CS: Certainty score
1.4 **CYP2C19-CLOPIDOGREL**

### 1.4.1 Publication selection

**Risk analysis:** [https://kennisbank.knmp.nl/files/farmacogenetica/2548-2549-2550.PDF](https://kennisbank.knmp.nl/files/farmacogenetica/2548-2549-2550.PDF)

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

| Steps performed systematically to select suitable publication(s) form which extraction is performed | Publication(s) selection |
|---|---|
| 1 Publications reporting predicted phenotype group: quality score 4, powered on mortality | **Study** | **Conclusion** |
| Niu X et al. (76) | Not powered on mortality. Not selected. |
| Jang JS et al. (77) | Not powered on mortality. Not selected. |
| Pan Y et al. (78) | Not powered on mortality. Not selected. |
| Sorich MJ et al. (79) | Not powered on mortality. Not selected. |
| Mao L et al. (80) | Not powered on mortality. Not selected. |
| Li Y et al. (81) | Not powered on mortality. Not selected. |
| Holmes MV et al. (82) | Not powered on mortality. Not selected. |
| Liu YP et al. (83) | Not powered on mortality. Not selected. |
| Mega JL et al. (84) | Not powered on mortality. Not selected. |
| Simon T et al. (85) | Not powered on mortality. Not selected. |
| Collet JP et al. (86) | Not powered on mortality. Not selected. |
| Simon T et al. (87) | Not powered on mortality. Not selected. |
| Shen DL et al. (88) | Not powered on mortality. Not selected. |
| Mega JL et al. (89) | Not powered on mortality. Not selected. |
## Conclusion:
No publication was selected therefore we will continue to the next step.

| Study                  | Conclusion                                      |
|------------------------|--------------------------------------------------|
| Geisler T et al.(90)   | Not powered on mortality. Not selected.          |
| Chen BL et al.(91)     | Not powered on mortality. Not selected.          |
| Kim KA et al. (92)     | Not powered on mortality. Not selected.          |
| Malek LA et al.(93)    | Not powered on mortality. Not selected.          |
| Trenk D et al. (94)    | Not powered on mortality. Not selected.          |
| Fontana P et al.(95)   | Not powered on mortality. Not selected.          |
| Hulot JS et al.(96)    | Not powered on mortality. Not selected.          |

### 2 Publications reporting predicted phenotype group: quality score 4

| Study                  | Conclusion                                      |
|------------------------|--------------------------------------------------|
| Niu X et al. (76)      | Usable risk data: Yes                           |
|                        | Representative: No, predominantly studies performed in Asia |
|                        | Not selected.                                    |
| Jang JS et al. (77)    | Usable risk data: Yes (genetic variant in most studies is *2) |
|                        | Representative: Yes                             |
|                        | Not selected. Another meta-analysis is more recent (2012) |
| Pan Y et al. (78)      | Usable risk data: Yes (*2, 3, 17, 1)            |
|                        | Representative: No                             |
|                        | Not selected.                                   |
| Sorich MJ et al. (79)  | Usable risk data: Yes (*2, 3, 17, 1)            |
|                        | Representative: Yes                             |
|                        | Most recent meta-analysis (2014). Selected for extraction of untested groups. |
| Mao L et al. (80)      | Usable risk data: Yes (loss of function *2-*8)  |
|                        | Representative: Yes                             |
| Study                                      | Usable risk data                          | Representative | Selection  | Notes                                                                 |
|-------------------------------------------|-------------------------------------------|----------------|------------|-----------------------------------------------------------------------|
| Li Y et al. (81)                          | Usable risk data: No (only *17)           | Yes            | Not selected. | Another meta-analysis is more recent (2013).                          |
| Holmes MV et al. (82)                     | Usable risk data: Yes (any loss of function allele) | Yes            | Not selected. | Another meta-analysis is more recent (2011).                          |
| Liu YP et al. (83)                        | Usable risk data: Yes (Any loss of function allele) | Yes            | Not selected. | Another meta-analysis is more recent (2011).                          |
| Mega JL et al. (84)                       | Usable risk data: Yes (only *2 loss of function) | Yes            | Not selected. | Another meta-analysis is more recent.                                 |
| Simon T et al. (85)                       | Usable risk data: No                      | No             | Not selected. |                                                                        |
| Collet JP et al. (86)                     | Usable risk data: Yes (only *2 loss of function) | No             | Not selected. |                                                                        |
| Simon T et al. (87)                       | Usable risk data: Yes (multiple loss of function alleles) | Yes            | Not selected. | Included in meta-analysis by Sorich MJ et al.                         |
| Shen DL et al. (88)                       | Representative: No, Chinese population.    | No             | 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.

| 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. |
| Study Authors               | Status                              |
|----------------------------|-------------------------------------|
| 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. |
| Fontana P et al. (117)     | Not powered on mortality. Not selected. |
| Giusti B et al. (118)      | Not powered on mortality. Not selected. |
| Brandt JT et al. (119)     | Not powered on mortality. Not selected. |
## Conclusion:

No publication was selected therefore we will continue to the next step.

| Publications reporting predicted phenotype group: quality score 3 | Study | Conclusion |
| --- | --- | --- |
| Lee CR et al. (97) | Usable risk data: Yes (MACE)  
Representative: Yes  
Selected for extraction of tested groups. | |
| Zhong Z et al. (98) | Representative: No, Chinese patients.  
Not selected. | |
| Wu Y et al. (99) | Representative: No, Chinese patients.  
Not selected. | |
| Cavallari LH et al. (100) | Usable risk data: Yes  
Representative: Yes  
Selected for extraction of tested groups. | |
| Lin Y et al. (101) | Representative: No, Chinese patients.  
Not selected. | |
| Deiman BA et al. (102) | Usable risk data: No, only PM selected.  
Representative: Yes  
Not selected. | |
| Wang Y et al. (103) | Representative: No, Chinese patients.  
Not selected. | |
| Ogawa H et al. (104) | Representative: No, Japanese patients.  
Not selected. | |
| Xiong R et al. A (105) | Representative: No, Chinese patients.  
Not selected. | |
| Xie X et al. (106) | Representative: No, Chinese patients.  
Not selected. | |
| Reference                        | Description                                      |
|---------------------------------|--------------------------------------------------|
| Collet JP et al. (107)           | Representative: No, only young and male patients selected. <br>Usable risk data: No <br>Not selected. |
| Bonello-Palot N et al. (108)     | Usable risk data: No. Not genotype-guided. <br>Representative: Yes. <br>Not selected. |
| Shuldiner AR et al. (109)        | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Frére C et al. (110)             | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Aleil B et al.(111)              | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Sibbing D et al. (112)           | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Brackbill ML et al. (113)        | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Giusti B et al. (114)            | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Umemura K et al. (115)           | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Frére C et al. (116)             | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Fontana P et al. (117)           | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Giusti B et al. (118)            | Usable risk data: No. Not genotype-guided. <br>Not selected. |
| Brandt JT et al. (119)           | Usable risk data: No. Not genotype-guided. <br>Not selected. |

**Conclusion:**<br>We have selected 2 publications (Lee CR et al.(97)and Cavallari LH et al. (100)) for the extraction of data for tested groups.
1.4.2 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 (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 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 = 0.031467086 for non-actionable CYP2C19 UM and EMs. These are given a certainty score of 3.

1.4.3 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.

1.4.4 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.

| Actionability | Untested | Ref | CS | Tested | Ref | CS |
|---------------|----------|-----|----|--------|-----|----|
| Clopidogrel   | CYP2C19 EM | No  | 0.031467084 (79) | 3   | 0.031467084 (79) | 3   |

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.

1.4.5 Conclusion of selected publications and absolute risks extracted:
| Drug       | Cytochrome P450 | Metabolism | MIC (µg/mL) | CIs       | CS |
|------------|------------------|------------|-------------|-----------|----|
| 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
### 1.5 **UGT1A1-IRINOTECAN**

#### 1.5.1 Publication selection

**Risk analysis:** [https://kennisbank.knmp.nl/files/farmacogenetica/1691-1692.PDF](https://kennisbank.knmp.nl/files/farmacogenetica/1691-1692.PDF)

| Steps performed systematically to select suitable publication(s) form which extraction is performed | Publication(s) selection |
| --- | --- |
| 1 | Publications reporting predicted phenotype group: quality score 4, powered on mortality |
|  | **Study** | **Conclusion** |
| Chen X et al. (121) | Not powered on mortality. Not selected. |
| Liu XH et al. (122) | Not powered on mortality. Not selected. |
| Han FF et al. (123) | Not powered on mortality. Not selected. |
| Chen YJ et al. (124) | Not powered on mortality. Not selected. |
| Liu X et al. (125) | Not powered on mortality. Not selected. |
| Hu ZY et al. (126) | Not powered on mortality. Not selected. |
| Hu ZY et al. (127) | Not powered on mortality. Not selected. |
| Hoskins JM et al. (128) | Not powered on mortality. Not selected. |
| Dias MM et al. (129) | Not powered on mortality. Not selected. |
| Liu X et al. (130) | Not powered on mortality. Not selected. |
| Dias MM et al. (131) | Not powered on mortality. Not selected. |
| Denlinger CS et al. (132) | Not powered on mortality. Not selected. |

**Conclusion:**
No publication was selected therefore we will continue to the next step.

| 2 | Publications reporting predicted phenotype group: quality score 4 |
| --- | --- |
|  | **Study** | **Conclusion** |
| Chen X et al. (121) | Usable risk data: Yes Representative: No, Asian patients. Not selected. |
| Reference       | Usable risk data | Representative | Notes                                                                 |
|-----------------|------------------|----------------|----------------------------------------------------------------------|
| Liu XH et al. (122) | Yes              | No             | less than 50% of the studies performed in Caucasian population.          |
| Han FF et al. (123)  | No (only ORs)    | No             | Asian patients. Ser.                                               |
| Chen YJ et al. (124) | No               | No             | Asian patients. Ser.                                               |
| Liu X et al. (125)    | Yes              | Yes            | Selected for extraction of untested groups.                           |
| Hu ZY et al. (126)    | No (only ORs)    | Yes            | Ser.                                                               |
| Hu ZY et al. (127)    | Yes              | Yes            | Ser.                                                               |
| Hoskins JM et al. (128) | No, only looks at *28/*28 vs. *1/*1 + *28/*1 | Yes | Not selected. Another meta-analysis is more recent. |
| Dias MM et al. (129)   | No               |                | Ser.                                                               |
| Liu X et al. (130)    | No               | Yes            | Not selected.                                                       |
| Dias MM et al. (131)    | No               |                | Ser.                                                               |
| Denlinger CS et al. (132)| No           |                | Ser.                                                               |

Conclusion:
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.

| Study                          | Conclusion                                      |
|-------------------------------|-------------------------------------------------|
| Lu CY et al. (133)            | Not powered on mortality. Not selected.         |
| Goetz MP et al. (134)         | Not powered on mortality. Not selected.         |
| Kweekel DM et al. (135)       | Not powered on mortality. Not selected.         |
| Liu CY et al. (136)           | Not powered on mortality. Not selected.         |
| Lankisch TO et al. (137)      | Not powered on mortality. Not selected.         |
| Minami H et al. (138)         | Not powered on mortality. Not selected.         |
| Stewart CF et al. (139)       | Not powered on mortality. Not selected.         |
| Côté JF et al. (140)          | Not powered on mortality. Not selected.         |
| Ramchandani RP et al. (141)   | Not powered on mortality. Not selected.         |
| Zárate Romero R et al. (142)  | Not powered on mortality. Not selected.         |
| de Jong FA et al. (143)       | Not powered on mortality. Not selected.         |
| Toffoli G et al. (144)        | Not powered on mortality. Not selected.         |
| Han JY et al. (145)           | Not powered on mortality. Not selected.         |
| McLeod HL et al. (146)        | Not powered on mortality. Not selected.         |
| Massacesi C et al. (147)      | Not powered on mortality. Not selected.         |
| Wright MA et al. (148)        | Not powered on mortality. Not selected.         |
| Kweekel DM et al.             | Not powered on mortality. Not selected.         |
| Soepenberg O et al. (149)     | Not powered on mortality. Not selected.         |
| Study                        | Conclusion                                      |
|-----------------------------|-------------------------------------------------|
| Zhou Q et al. (150)         | Not powered on mortality. Not selected.          |
| Carlini LE et al. (151)     | Not powered on mortality. Not selected.          |
| Kitagawa C et al. (152)     | Not powered on mortality. Not selected.          |
| Marcuello E et al. (153)    | Not powered on mortality. Not selected.          |
| Rouits E et al. (154)       | Not powered on mortality. Not selected.          |
| Paoluzzi L et al. (155)     | Not powered on mortality. Not selected.          |
| Sai K et al. (156)          | Not powered on mortality. Not selected.          |
| Innocenti F et al. (157)    | Not powered on mortality. Not selected.          |
| Font A et al. (158)         | Not powered on mortality. Not selected.          |
| Mathijssen RH et al. (159)  | Not powered on mortality. Not selected.          |
| Iyer L et al. (160)         | Not powered on mortality. Not selected.          |
| Ando Y et al. (161)         | Not powered on mortality. Not selected.          |

**Conclusion:**
No publication was selected therefore we will continue to the next step.

| Study                        | Conclusion                                      |
|-----------------------------|-------------------------------------------------|
| Lu CY et al. (133)          | Representative: No, Taiwanese patients. Not selected. |
| Goetz MP et al. (134)       | Representative: Yes Usable risk data: No. Not selected. |
| Kweekel DM et al. (135)     | Representative: Yes Usable risk data: No, not genotype-guided. Not selected. |
| Liu CY et al. (136)         | Representative: No, Chinese patients. Not selected. |
| Lankisch TO et al. (137)    | Representative: Yes                                |
| Study Authors          | Usable Risk Data                      | Representative                                      |
|------------------------|---------------------------------------|-----------------------------------------------------|
| Minami H et al. (138)  | No, not genotype-guided                | Not selected.                                        |
| Stewart CF et al. (139)| No, not genotype-guided                | Not selected.                                        |
| Côté JF et al. (140)   | No, not genotype-guided                | Not selected.                                        |
| Ramchandani RP et al. (141) | No, not genotype-guided   | Not selected.                                        |
| Zárate Romero R et al. (142) | No, not genotype-guided   | Not selected.                                        |
| de Jong FA et al. (143) | No, not genotype-guided                | Not selected.                                        |
| Toffoli G et al. (144) | No, not genotype-guided                | Not selected.                                        |
| Han JY et al. (145)    | No, not genotype-guided                | Not selected.                                        |
| McLeod HL et al. (146) | No, not genotype-guided                | Not selected.                                        |
| Massacesi C et al. (147) | No, not genotype-guided   | Not selected.                                        |
| Wright MA et al. (148) | No, not genotype-guided                | Not selected.                                        |
| Kweekel DM et al.      | No, not genotype-guided                | Not selected.                                        |
| Soepenberg O et al. (149)| No, not genotype-guided   | Not selected.                                        |
| Zhou Q et al. (150)    | 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**

| Search strategy pubmed                                                                 | Date literature search |
|---------------------------------------------------------------------------------------|------------------------|
| Irinotecan[Title] AND (UGT1A1[Title] OR Pharmacogene[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.
1.5.2 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 0.00949 = 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 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 0.1865 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 diarrhea 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 diarrhea is 0.001363473 (section treatment related deaths sum of patients death of diarrhea/total patients = 19/13935) . Therefore, risk of death as a result of grade 3 diarrhea 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 diarrhea 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 diarrhea is 0.001363473 (section treatment related deaths sum of patients death of diarrhea/total patients = 19/13935) (162). Therefore, risk of death as a result of grade 3 diarrhea is 0.1473 x 0.0013 = 0.00020088 for non-actionable *1/*28 and IM. These are given a certainty score of 3.

1.5.3 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 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

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grade 3 neutropenia is $0.3525 \times 0.00949 = 0.003344836$ 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 $0.2155 \times 0.001 = 0.000293852$ for untested *28/*28 and PM. These are given a certainty score of 3.

1.5.4 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).

1.5.5 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

1.5.6 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  | 0.000200888 (125) | 3 | 0.000200888 (125) | 3 |
| Irinotecan    | UGT1A1 *28/*28 | yes | 0.000293852 (125) | 3 | 0.000151267 - | 0 |
| Irinotecan    | UGT1A1 IM | no  | 0.000200888 (125) | 3 | 0.000200888 (125) | 3 |
| Irinotecan    | UGT1A1 PM | yes | 0.000293852 (125) | 3 | 0.000151267 - | 0 |

Ref: Reference; CS: certainty score
### 1.5.7 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
## 1.6 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** | 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) |
| **TPMT-mercaptopurine** | | | |
| **TPMT-thiopurine** | | | |
| **DPYD-capecitabine** | 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) |
| **DPYD-fluorouracil** | | | |
| **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 | 0.9% | A post marketing survey of irinotecan into severe adverse effects and treatment-related deaths. The number of deaths from severe adverse drug reactions whose causal relationship with irinotecan could not be ruled out was 176 (1.3%) of the 13 935 patients. Of the 176 | (162) |
| | Grade≥3 diarrhea | 0.1% | | |

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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%.
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**Supplementary Table 4** Costs used in the decision analytic model

| Input                        | Regimen | Dose form | Cost       | Source                                                                 |
|------------------------------|---------|-----------|------------|------------------------------------------------------------------------|
| PGx test for *TMPT*          | -       | -         | €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: Ref van der wouden et al. *(unpublished)* (1) Salary: Clinical Pharmacists as standardized in Dutch Academic Hospitals in 2019 (2) |
| Physician time               | -       | -         | €4.28 per 6 minutes | Time: Estimation based on Ref. *(unpublished)* (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 | 2x tablet 75mg | €0.34 per tablet | Medicijnkosten.nl (3) |
| Azathioprine 10% (PM)        | 1dd 0.5mg/kg | 1x tablet 50mg | €0.19 per tablet | Medicijnkosten.nl (3) |
| Capecitabine 100% (GAS 2)   | 2dd 1250mg/m² for 2 weeks. 1 | 4x tablet 500mg | €1.24 per tablet | Medicijnkosten.nl (3) |
| Drug | Dosage | Cost per dose | Manufacturer |
|------|--------|---------------|--------------|
| Capecitabine 50% (GAS 1.5, 1) | 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) | 1x tablet 75mg € 0.04 per tablet | Medicijnkosten.nl (3) |
| Clopidogrel 200% (IM) | 2x tablet 75mg € 0.04 per tablet | Medicijnkosten.nl (3) |
| Clopidogrel alternative 1 (PM, ACS -25%) | 2 x tablet 90mg € 1.24 per tablet | Medicijnkosten.nl (3) |
| Clopidogrel alternative 2 (PM, ACS -25%) | 1 x tablet 10mg € 1.63 per tablet | Medicijnkosten.nl (3) |
| Clopidogrel alternative 3 (PM, TIA -50%) | 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) | 1 x vial 50mg/mL 20mL € 6.81 per dose | Medicijnkosten.nl (3) |
| 5-FU 50% (GAS 1.5, 1) | 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) | 1 x vial 20mg/mL 25mL and 1 x vial 20mg/mL 5 mL € 856.25 per dose | Medicijnkosten.nl (3) |
| Drug                          | Strength | Route | Dosage | Formulation | Price per dose | Source                        |
|-------------------------------|----------|--------|--------|-------------|----------------|-------------------------------|
| Irinotecan 70% (*28/*28, PM)  | 245mg/m² | every 3 weeks | 1 x vial 20mg/ml 25mL | € 712.74 per dose | Medicijkosten.nl (3) |
| Mercaptopurine 100%          | 1 dd 1.5mg/kg | 2 x tablet 50mg | € 2.68 per tablet | Medicijkosten.nl (3) |
| Mercaptopurine 50% (IM)      | 1 dd 0.75mg/kg | 1 x tablet 50mg | € 2.68 per tablet | Medicijkosten.nl (3) |
| Mercaptopurine 10% (PM)      | 1 dd 0.15mg/kg | 15mg/mL 1mL vial | € 16.35 per dose | Medicijkosten.nl (3) |
| Tioguanine 100% (EM)         | 1 dd 0.3mg/kg | 1 x capsule 21mg | € 2.98 per capsule | Medicijkosten.nl (3) |
| Tioguanine 75% (IM)          | 1 dd 0.225mg/kg | 1 x capsule 16mg | € 2.75 per capsule | Medicijkosten.nl (3) |
| Tioguanine 6% (PM)           | 1 dd 0.018mg/kg | 1 x capsule 10mg | € 2.49 per capsule | Medicijkosten.nl (3) |

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