

Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 update

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Table of Contents

Guideline Updates.....	3
Literature Review.....	3
Genetic Test Interpretation	4
Other considerations	6
Level of Evidence	7
Strength of Recommendation	7
Resources to Incorporate Pharmacogenetics into an Electronic Health Record with Clinical Decision Support.....	8
Supplemental Table S1. Evidence linking <i>DPYD</i> genotype with DPD phenotype and dihydropyrimidine toxicity	11
References.....	65

Guideline Updates

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *DPYD* genotypes and the dosing of fluoropyrimidines is published in full on [https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/\(1\)](https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/(1)) and at pharmgkb.org. Relevant information will be reviewed periodically and updated guidelines published online.

Literature Review

2013 guideline

A literature search of the PubMed® database (1966 to March 2013) using the keywords ((DPD OR DPYD OR Dihydropyrimidine Dehydrogenase) AND (fluorouracil OR 5-FU OR fluoropyrimidines OR capecitabine OR tegafur) AND genotype) was performed and results were limited to those available in English. Further articles were found via the reference sections of reviews. Using these search terms, 104 publications were identified. Study inclusion criteria included publications that included analyses for the association between *DPYD* genotypes (c.1905+1G>A , c.1679T>G, and c.2846A>T) and metabolism of dihydropyrimidines and adverse drug events or clinical outcomes. Non-English manuscripts were excluded. Following application of these inclusion criteria, 30 publications were reviewed and included in the evidence tables

2017 guideline

We searched PubMed® database as described above between 1966 and March 2017. The 2013 literature review was repeated to include all known *DPYD* genotypes. Using these search terms, 150 publications were identified. Following application of the inclusion criteria, 49 publications were reviewed and included in the evidence tables. An additional 43 studies were identified from the reference sections of reviews and other published paper, and included in the evidence tables, bringing the total included studies to 92 (**Supplemental Table S1**).

Genetic Test Interpretation

While some *DPYD* variants have been assigned a (*) allele, this nomenclature has not been updated to include more recently identified decreased function variants. As a consequence, only a minority of *DPYD* variants has a (*) allele designation. Furthermore, the (*) allele nomenclature is used for other drug metabolizing enzymes to designate haplotypes. Due to the size of *DPYD*, the gene encompasses several haplotype blocks (2, 3) with low linkage disequilibrium between variants located in different haplotype blocks. As a consequence, it is not possible to reliably determine full haplotypes that incorporate genotypes for common polymorphisms (e.g. c.85T>C, c.2194G>A) across the entire gene. Therefore, any (*) alleles used for *DPYD* generally do not refer to haplotypes but only to a genotype at one specific SNP locus. To avoid confusion with (*) allele nomenclature used for haplotypes of other drug metabolizing enzymes, the preferred nomenclature for *DPYD* variants is therefore the use of rs# or HGVS nomenclature.

Test results for *DPYD* do not report a diplotype for the entire gene, but genotypes for individual SNP loci. Importantly, however, all currently established toxicity-associated decreased/no function *DPYD* variants have a low population frequency (<5%) and are observed most frequently in individuals without a second decreased/no function variant. Therefore, in patients who carry two different decreased/no function variants, for the test interpretation, it is assumed that the two variants with an impact on DPD activity are located on different gene copies. For patients, in whom novel *DPYD* variants with suspected deleterious impact are detected in combination with known decreased/no function variants, this assumption may not be correct. In such a case, a phenotyping test may be helpful to determine enzyme activity, or genotyping of relatives (parents, siblings, and offspring) to determine segregation patterns. In addition, a genetic test may also include genotyping of other, common *DPYD* variants (e.g. c.85T>C, c.1627A>G, c.2194G>A). If this is case, a patient may be heterozygous for multiple of these variants and it cannot be determined which alleles are located on the same gene copy. However, based on current data, none of these common variants have a clinically relevant impact in the context of 5-fluorouracil related toxicity. The exact haplotype configuration of these

normal function variants is thus not required for the test interpretation. Therefore, to calculate the *DPYD* gene activity score, only the variant activity scores for the two variants with the lowest activity score is considered. For example, if a patient is a heterozygous carrier of a decreased function variant (e.g. c.1129–5923C>G) and two normal function variants (e.g. c.85T>C and c.1627A>G), the variant activity score of 0.5 for c.1129–5923C>G would be considered for one gene copy, and an activity score of 1 for the second gene copy, resulting in a total gene activity score of 1.5.

The dosing recommendations in this guideline are specific for variant alleles in which there are clear data linking the *DPYD* genotype to fluoropyrimidine toxicity (c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129–5923C>G) (**Supplementary Table S1**). Several other variants have been reported to be associated with reduced enzyme activity and/or linked to fluoropyrimidine toxicity, albeit with somewhat weaker evidence (see ***DPYD* Allele Functionality Table (4)**, “moderate evidence supporting function”). While most of these variants are rare (see ***DPYD* Allele Frequency Table (4)**), the decreased function variant rs115232898 (c.557T>C, p.Y186C) is relatively common in individuals of African ancestry and has been observed in case reports of patients with severe 5-fluorouracil related toxicity (5, 6).

On the other hand, several *DPYD* variants that are relatively common in the population have strong or moderate evidence that they do not impact DPD function in a clinically relevant manner in the context of 5-fluorouracil related toxicity. For rs1801159 (*5, c.1627A>G, p.I543V) and rs1801265 (*9A, c.85T>C, p.C29R) none of the large cohort and case-control studies observed a significant association with toxicity or reduced DPD activity (see **Supplemental Table S1**). For other variants, associations with toxicity have been observed in single studies, but could not be reproduced in a majority of studies (rs1801160, *6, c.2194G>A, p.V732I; rs2297595, c.496T>C, p.M166V) or by meta-analysis (rs1801158, *4, c.1601G>A, p.S534N) (see **Supplemental Table S1**). Based on current knowledge, a fluorouracil dose adaptation in carriers of these variants is thus not warranted.

Many of the variants listed in the “in vitro data only and/or limited clinical/ex vivo data” category (see **DPYD Allele Functionality Table (4)**) as decreased or no function variants have a very low (<0.5%) allele frequency in the populations studied (see **DPYD Allele Frequency Table (4)**) and to date, there are no studies linking these variant alleles directly to toxicity related to fluoropyrimidines. Their functional effect was evaluated by comparison of their in vitro activity to the *in vitro* activity of known toxicity-associated *DPYD* variants: All variants with *in vitro* activity similar to c.1905+1G>A and c.1679T>G were categorized as “no function” variants; variants with *in vitro* activity greater than that of known “no function” variants but equal to or lower than the *in vitro* activity of c.2846A>T were classified as “decreased function” variants.

Several variants listed in the “unclear or conflicting data supporting function” category had *in vitro* DPD activity (i.e. homozygous expression of the variant) that was significantly lower than wildtype activity, but the magnitude of the decrease was smaller than for any established toxicity-associated variant. For these variants, it is currently not known if the decrease in DPD activity observed *in vitro* has a clinically relevant impact on 5-fluorouracil toxicity. At the time of writing, these variants would thus not be actionable for a reduction of the starting dose in fluoropyrimidine-based therapies.

Other considerations

Several other genes may influence responses to 5-fluorouracil (7, 8), in particular genes of the folate pathway. The most well-studied of these are *MTHFR* and *TYMS*, although to date for *TYMS* the underlying causal variants of associations (9) and their clinical utility (10) are unclear, and associations have been inconsistent for *MTHFR* (10). Therefore, predictive dosing strategies for these genes have yet to be successfully applied. Similarly, a recently identified association of a variant (rs17822471) in *ABCC11*, a transporter of 5-fluorouracil metabolites, with fluoropyrimidine-related leukopenia requires further investigation (11, 12). In the context of capecitabine-based therapies, genes in the capecitabine activation pathway have also been studied, most notably *CDA*, *CES1* and *CES2* (13, 14). While some associations have been reported, these results have not been sufficiently replicated to determine potential genotype-based therapeutic strategies.

Furthermore, Fernandez-Rozadilla *et al* performed a genome-wide association study on 221 colorectal cancer patients (including a validation set of 791 patients) that had been treated with a 5-fluorouracil-based regimen (15). Seven SNPs (rs16857540 (*NLG1*), rs2465403 (*COLEC10*), rs10876844 (*OR10AE3P*, *PSMB2P*), rs10784749, rs17626122 (*PARD3B*), rs7325568 and rs4243761) showed evidence of association with adverse drug reactions. They also evaluated the association signals for seven SNPs that had been linked to 5-fluorouracil-related toxicity in the literature (rs1801159 and rs1801265 (*DPYD*), rs18010919 (*UMPS*), rs1801133 (*MTHFR*), rs34743033, rs34489327 (*TYMS*), rs1695 (*GSTP1*)). Four of these variants had good proxy SNPs in the study, but none of them showed a statistically significant association. Some of the identified associations underscore the potential importance of other genes that may contribute increased risk of toxicity of 5-fluorouracil, although further studies are needed to determine their clinical utility.

Level of Evidence

The evidence summarized in **Supplemental Table S1** is graded using a scaled modified slightly from Valdes *et al* (16).

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Strength of Recommendation

CPIC's dosing recommendations (**Table 2, main manuscript**) are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken

into account include *in vivo* clinical outcome for reference drug, *in vivo* PK/PD for reference drug, and *in vitro* enzyme activity with probe substrate only.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents

(<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>):

Strong recommendation for the statement: “The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.”

Moderate recommendation for the statement: “There is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

The strength of the 5-fluorouracil dosing recommendations (**Table 2, main manuscript**) is based on the fact that some variants (c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129–5923C>G) clearly affect DPD activity, and DPD activity is clearly related to 5-fluorouracil clearance, and 5-fluorouracil exposure is associated with its toxic effects. Therefore, reduction of 5-fluorouracil dosage in patients with these variants can prevent severe and possibly life-threatening toxicities, as has been demonstrated for c.1905+1G>A (17). The strength of the capecitabine dosing recommendations is based on the fact that this prodrug of 5-fluorouracil is metabolized by DPD in the same manner.

Resources to Incorporate Pharmacogenetics into an Electronic Health Record with Clinical Decision Support

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (18-22). See

<https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/> for resources to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *DPYD* genotype results to guide fluoropyrimidine dosing in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (23, 24). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the “person level” rather than at the date-centric “encounter level”. Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (18, 25).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *DPYD* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>) (26).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also

providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>).

Supplemental Table S1. Evidence linking *DPYD* genotype with DPD phenotype and dihydropyrimidine toxicity

<i>DPYD</i> *allele rsID nucleotide change ^a protein change ^b	Parameter	Major findings	References	Type of experimental model	Level of Evidence ^{c,d}
*2A rs3918290 c.1905+1G>A	Activity	AG is associated with decreased DPD activity as compared to GG	Supports Statement: Statistically Significant: Wei, <i>et al.</i> (1996)(27) Kuilenburg, <i>et al.</i> (2016)(28) Nie, <i>et al.</i> (2017)(29) Same Direction of Association: Sistonen, <i>et al.</i> (2014)(30)	Clinical, Ex vivo	Moderate
		Within cell lines, AA is associated with decreased DPD activity as compared to GG	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(31)	In vitro	High
		AA + AG were observed in individuals with decreased DPD activity	Supports Statement: Holopainen, <i>et al.</i> (1997)(32) Vreken, <i>et al.</i> (1997)(33) Van Kuilenburg, <i>et al.</i> (1997)(34) Ridge, <i>et al.</i> (1998)(35) Van Kuilenburg, <i>et al.</i> (1999)(36) van Kuilenburg, <i>et al.</i> (2001)(37) Johnson, <i>et al.</i> (2002)(38) Maring, <i>et al.</i> (2002)(39) van Kuilenburg, <i>et al.</i> (2002)(40) Van Kuilenburg, <i>et al.</i> (2002)(41) Al-Sanna'a, <i>et al.</i> (2005)(42)	Clinical, Ex vivo	High

			<p>Ezzeldin, <i>et al.</i> (2005)(43) Largillier, <i>et al.</i> (2006)(44) Magne, <i>et al.</i> (2007)(45) Loganayagam, <i>et al.</i> (2010)(46) van Kuilenburg, <i>et al.</i> (2010)(47) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Loganayagam, <i>et al.</i> (2010)(46)</p>		
	Dose	AG is associated with decreased capecitabine dose as compared to GG	<p>Supports Statement: Statistically Significant: Deenen, <i>et al.</i> (2011)(50)</p>	Clinical	Moderate
		Individuals with AG received a decreased dose of capecitabine	<p>Supports Statement: Joerger, <i>et al.</i> (2015)(51)</p>	Clinical	Weak
	Efficacy	AG is associated with a decreased acute lymphoblastic leukemia complete remission rate as compared to GG	<p>Supports Statement: Statistically Significant: Zhao, <i>et al.</i> (2016)(52)</p>	Clinical	Weak
		AA + AG are not associated with progression-free, disease-free, event-free or overall survival times or confirmed response rate as compared to GG	<p>McLeod, <i>et al.</i> (2010)(53) Deenen, <i>et al.</i> (2011)(50) Cai, <i>et al.</i> (2014)(54) Zhao, <i>et al.</i> (2016)(52)</p>	Clinical	Moderate
	Metabolism	AG is associated with decreased metabolism of fluorouracil as compared to GG	<p>Supports Statement: Statistically Significant: Boisdron-Celle, <i>et al.</i> (2007)(55) van Kuilenburg, <i>et al.</i> (2008)(56) Gentile, <i>et al.</i> (2016)(57)</p>	Clinical, Ex vivo	High

		Individuals with AG were observed to have decreased metabolism of fluorouracil	Supports Statement: Maring, <i>et al.</i> (2002)(58) Joerger, <i>et al.</i> (2015)(51)	Clinical	Moderate
	Toxicity	AA + AG are associated with increased risk or severity of fluoropyrimidine toxicity as compared to GG	Supports Statement: Statistically Significant (overall toxicity): Van Kuilenburg, <i>et al.</i> (2002)(59) Salgueiro, <i>et al.</i> (2004)(60) Boisdron-Celle, <i>et al.</i> (2007)(55) Schwab, <i>et al.</i> (2008)(61) Deenen, <i>et al.</i> (2011)(50) Lee, <i>et al.</i> (2014)(62) Toffoli, <i>et al.</i> (2015)(63) Statistically Significant (myelosuppression): Schwab, <i>et al.</i> (2008)(61) Kleibl, <i>et al.</i> (2009)(64) Kristensen, <i>et al.</i> (2010)(65) Rosmarin, <i>et al.</i> (2014)(66) Cai, <i>et al.</i> (2014)(54) Statistically Significant (hand-foot syndrome): Cai, <i>et al.</i> (2014)(54) Statistically Significant (diarrhea): Deenen, <i>et al.</i> (2011)(50) Cai, <i>et al.</i> (2014)(54) Statistically Significant (mucositis): Schwab, <i>et al.</i> (2008)(61)	Clinical	High

			<p>Kleibl, <i>et al.</i> (2009)(64) Statistically Significant (hepatotoxicity): Zhao, <i>et al.</i> (2016)(52) Statistically Significant (infection): Zhao, <i>et al.</i> (2016)(52) Same Direction of Association (overall toxicity): Braun, <i>et al.</i> (2009)(67) Dhawan, <i>et al.</i> (2013)(68) Rosmarin, <i>et al.</i> (2014)(66) Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3) Boige, <i>et al.</i> (2016)(69) Same Direction of Association (neutropenia): McLeod, <i>et al.</i> (2010)(53) Does Not Support Statement: Amstutz, <i>et al.</i> (2009)(2) McLeod, <i>et al.</i> (2010)(53)</p>		
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		AA + AG were observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: Wei, <i>et al.</i> (1996)(27) Van Kuilenburg, <i>et al.</i>(1997)(34) van Kuilenburg, <i>et al.</i> (2000)(70) van Kuilenburg, <i>et al.</i> (2001)(37) Raida, <i>et al.</i> (2001)(71) Johnson, <i>et al.</i> (2002)(38) Maring, <i>et al.</i> (2002)(58) Van Kuilenburg, <i>et al.</i> (2002)(41) Steiner, <i>et al.</i> (2005)(72) Ezzeldin, <i>et al.</i> (2005)(43) Largillier, <i>et al.</i> (2006)(44) Morel, <i>et al.</i> (2006)(73) Saif, <i>et al.</i> (2007)(74) Salgado, <i>et al.</i> (2007)(75) Magne, <i>et al.</i> (2007)(45) Sulzyc-Bielicka, <i>et al.</i>(2008)(76) Gross, <i>et al.</i> (2008)(77) Loganayagam, <i>et al.</i> (2010)(46) Boige, <i>et al.</i> (2010)(78) Ceric, <i>et al.</i> (2010)(79) van Kuilenburg, <i>et al.</i> (2010)(47) Savva-Bordalo, <i>et al.</i> (2010)(80) Cellier, <i>et al.</i> (2011)(147) Loganayagam, <i>et al.</i> (2013)(13) Suarez Martinez-Falero, <i>et al.</i> (2014)(81) Joerger, <i>et al.</i> (2015)(51) Thomas, <i>et al.</i> (2016)(48) Roberto, <i>et al.</i> (2017)(82)</p>	Clinical	High
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<p>*13 rs55886062 c.1679T>G p.I560S</p>	Activity	GT is associated with decreased DPD activity as compared to TT	<p>Supports Statement: Statistically Significant: Offer, <i>et al.</i>(2013)(5) Nie, <i>et al.</i> (2017)(29) Same Direction of Association: Sistonen, <i>et al.</i> (2014)(30)</p>	Clinical, Ex vivo	Moderate
		Within cell lines, GG is associated with decreased DPD activity was compared to TT	<p>Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(31)</p>	In vitro	High
		GT was observed in individuals with decreased DPD activity	<p>Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Johnson, <i>et al.</i> (2002)(38) van Kuilenburg, <i>et al.</i> (2002)(40) Ezzeldin, <i>et al.</i> (2005)(43) Thomas, <i>et al.</i> (2016)(48)</p>	Clinical, Ex vivo	High
	Toxicity	GT is associated with increased risk or severity of fluoropyrimidine toxicity as compared to TT	<p>Supports Statement: Same Direction of Association (overall toxicity): Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3) Lee, <i>et al.</i> (2014)(62) Toffoli, <i>et al.</i> (2015)(63) Does Not Support Statement: Amstutz, <i>et al.</i> (2009)(2) Deenen, <i>et al.</i> (2011)(50) Boige, <i>et al.</i> (2016)(69)</p>	Clinical	High
		GT was observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Johnson, <i>et al.</i> (2002)(38) Ezzeldin, <i>et al.</i> (2005)(43)</p>	Clinical	High

			<p>Morel, <i>et al.</i> (2006)(73) Loganayagam, <i>et al.</i> (2010)(46) Cellier, <i>et al.</i> (2011)(83) Loganayagam, <i>et al.</i> (2013)(13) Dhelens, <i>et al.</i> (2016)(84) Thomas, <i>et al.</i> (2016)(48)</p>		
rs67376798 c.2846A>T p.D949V	Activity	The AT genotype/the T allele is associated with decreased DPD activity as compared to the AA genotype	Supports Statement: Statistically Significant: Seck, <i>et al.</i> (2005)(85) Same Direction of Association: Sistonen, <i>et al.</i> (2014)(30) Kuilenburg, <i>et al.</i> (2016)(28) Nie, <i>et al.</i> (2017)(29) Does Not Support Statement: Offer, <i>et al.</i> (2013)(5)	Clinical, Ex vivo	Moderate
		Within cell lines, the T allele is associated with decreased DPD activity as compared to AA	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86) Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	High
		The AT genotype/the T allele was observed in individuals with decreased DPD activity	Supports Statement: van Kuilenburg, <i>et al.</i> (2002)((40) Loganayagam, <i>et al.</i> (2010)(46) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Loganayagam, <i>et al.</i> (2010)(46)	Clinical, Ex vivo	Moderate

	Dose	The AT genotype is associated with decreased capecitabine dose as compared to the AA genotype	Supports Statement: <i>Statistically Significant:</i> Deenen, <i>et al.</i> (2011)(50)	Clinical	Moderate
	Efficacy	The AT genotype is not associated with disease-free survival as compared to the AA genotype	Lee, <i>et al.</i> (2014)(62)	Clinical	Moderate
	Metabolism	The AT genotype is associated with decreased metabolism of fluorouracil as compared to the AA genotype	Supports Statement: <i>Statistically Significant:</i> Boisdron-Celle, <i>et al.</i> (2007)(55) <i>Same Direction of Association:</i> Gentile, <i>et al.</i> (2016)(57)	Clinical, Ex vivo	Moderate
	Toxicity	The AT genotype/the T allele is associated with increased risk or severity of fluoropyrimidine toxicity as compared to the AA genotype	Supports Statement: <i>Statistically Significant (overall toxicity):</i> Boisdron-Celle, <i>et al.</i> (2007)(55) Schwab, <i>et al.</i> (2008)(61) Deenen, <i>et al.</i> (2011)(50) Rosmarin, <i>et al.</i> (2014)(66) Lee, <i>et al.</i> (2014)(62) Toffoli, <i>et al.</i> (2015)(63) Boige, <i>et al.</i> (2016)(69) <i>Statistically Significant (diarrhea):</i> Deenen, <i>et al.</i> (2011)(50) Joerger, <i>et al.</i> (2015)(51)	Clinical	High

			<p>Same Direction of Association (overall toxicity): Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3)</p>		
		The AT genotype/the T allele was observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: van Kuilenburg, <i>et al.</i> (2000)(70) Morel, <i>et al.</i> (2006)(73) Gross, <i>et al.</i> (2008)(77) Loganayagam, <i>et al.</i> (2010)(46) Obi, <i>et al.</i> (2011)(87) Cellier, <i>et al.</i> (2011)(83) Loganayagam, <i>et al.</i> (2013)(13) Thomas, <i>et al.</i> (2016)(48) Kuilenburg, <i>et al.</i> (2016)(28) Does Not Support Statement: Kristensen, <i>et al.</i> (2010)(65)</p>	Clinical	High
HapB3 rs75017182 + rs56038477 + rs56276561 c.1129-5923C>G + c.1236G>A (p.E412E) + c.483+18G>A	Activity	HapB3 is associated with decreased DPD activity	<p>Supports Statement: Statistically Significant: Sistonen, <i>et al.</i> (2014)(30) Nie, <i>et al.</i> (2017)(29) Same Direction of Association: Offer, <i>et al.</i> (2013)(5)</p>	Ex vivo, Clinical	Moderate
		HapB3 was observed in individuals with decreased DPD activity	<p>Supports Statement: van Kuilenburg, <i>et al.</i> (2010)(47) Meulendijks, <i>et al.</i> (2016)(88) Does Not Support Statement: Seck, <i>et al.</i> (2005)(85)</p>	Ex vivo	Moderate

	Dose	HapB3 was observed in individuals who required a fluoropyrimidine dose reduction	<p>Supports Statement: Meulendijks, <i>et al.</i> (2016)(88)</p> <p>Does Not Support Statement: Meulendijks, <i>et al.</i> (2016)(88)</p>	Clinical	Weak
	Toxicity	HapB3 is associated with increased risk or severity of fluoropyrimidine toxicity	<p>Supports Statement: Statistically Significant (overall toxicity): Amstutz, <i>et al.</i> (2009)(2) van Kuilenburg, <i>et al.</i> (2010)(47) Froehlich, <i>et al.</i> (2015)(3)</p> <p>Statistically Significant (diarrhea): Deenen, <i>et al.</i> (2011)(50)</p> <p>Statistically Significant (neutropenia): Lee, <i>et al.</i> (2016)(89)</p> <p>Same Direction of Association (overall toxicity): Schwab, <i>et al.</i> (2008)(61) Deenen, <i>et al.</i> (2011)(50) Rosmarin, <i>et al.</i> (2014)(66) Rosmarin, <i>et al.</i> (2015)(9) Lee, <i>et al.</i> (2016)(89) Boige, <i>et al.</i> (2016)(69)</p> <p>Does Not Support Statement: Kleibl, <i>et al.</i> (2009)(64) Loganayagam, <i>et al.</i> (2013)(13) Falvella, <i>et al.</i> (2015)(90)</p>	Clinical	High
		HapB3 was observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: van Kuilenburg, <i>et al.</i> (2010)(47) Meulendijks, <i>et al.</i> (2016)(88)</p>	Clinical	Weak

			Does Not Support Statement: Meulendijks, <i>et al.</i> (2016)(88)		
*2A (rs3918290, c.1905+1G>A) + rs67376798 (c.2846A>T, p.D949V) + *13 (rs55886062, c.1679T>G, p.I560S)	Toxicity	When the 1905+1 A allele and 2846 T allele are assessed together, with or without the 1679 G allele, they are associated with increased risk or severity of fluoropyrimidine toxicity	Supports Statement: Statistically Significant (overall toxicity): Morel, <i>et al.</i> (2006)(73) Saif, <i>et al.</i> (2013)(91) Statistically Significant (gastrointestinal events): Capitain, <i>et al.</i> (2008)(92)	Clinical	High
*2A (rs3918290, c.1905+1G>A) + rs67376798 (c.2846A>T, p.D949V) + *13 (rs55886062, c.1679T>G, p.I560S) + HapB3	Toxicity	When the 1905+1 A allele, the rs67376798 T allele and the HapB3 haplotype are assessed together, with or without the 1679 G allele, they are associated with increased risk or severity of fluoropyrimidine toxicity	Supports Statement: Statistically Significant (overall toxicity): Jennings, <i>et al.</i> (2013)(93) Froehlich, <i>et al.</i> (2015)(3)	Clinical	High
*2A (rs3918290, c.1905+1G>A) +	Toxicity	When the 1905+1 A allele, 2846 T allele, 1679 G allele and 1601 A allele are assessed	Supports Statement: Statistically Significant (overall toxicity): Loganayagam, <i>et al.</i> (2013)(13)	Clinical	Moderate

rs67376798 (c.2846A>T, p.D949V) + *13 (rs55886062, c.1679T>G, p.I560S) + *4 (rs1801158, c.1601G>A, p.S534N)		together they are associated with increased risk or severity of fluoropyrimidine toxicity			
*2A (rs3918290, c.1905+1G>A) + rs67376798 (c.2846A>T, p.D949V) + HapB3	Activity	When the 1905+1 A allele, 2846 T allele and the HapB3 haplotype are assessed together they are associated with decreased DPD activity	Supports Statement: <i>Statistically Significant:</i> Sistonen, <i>et al.</i> (2014)(30) Kuilenburg, <i>et al.</i> (2016)(28)	Clinical, Ex vivo	Moderate
*4 rs1801158 c.1601G>A p.S534N	Activity	AG/the A allele is associated with decreased DPD activity as compared to GG	Supports Statement: <i>Statistically Significant:</i> Seck, <i>et al.</i> (2005)(85) <i>Same Direction of Association:</i> Sistonen, <i>et al.</i> (2014)(30) Kuilenburg, <i>et al.</i> (2016)(28) Does Not Support Statement: Offer, <i>et al</i> (2013)(5)	Clinical, Ex vivo	Weak

		AG was observed in individuals with decreased DPD activity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Gross, <i>et al.</i> (2003)(94) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Ridge, <i>et al.</i> (1998)(35)	Clinical, Ex vivo	Weak
		Within cell lines, the A allele is associated with decreased DPD activity as compared to GG	Supports Statement: Statistically Significant: Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	Weak
		Within cell lines AA is associated with increased DPD activity as compared to the G allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(31)	In vitro	Weak
	Metabolism	AG is not associated with altered fluorouracil metabolism as compared to GG	Gentile, <i>et al.</i> (2016)(57)	Ex vivo	Weak
	Toxicity	The A allele is associated with increased risk or severity of fluoropyrimidine toxicity as compared to GG	Supports Statement: Same Direction of Association: Froehlich, <i>et al.</i> (2015)(3) Loganayagam, <i>et al.</i> (2013)(13) Rosmarin, <i>et al.</i> (2014)(66) Rosmarin, <i>et al.</i> (2015)(9) Does Not Support Statement: Schwab, <i>et al.</i> (2008)(61) Kleibl, <i>et al.</i> (2009)(64) Amstutz, <i>et al.</i> (2009)(2) Deenen, <i>et al.</i> (2011)(50) Froehlich, <i>et al.</i> (2015)(3)	Clinical	Weak

			Toffoli, <i>et al.</i> (2015)(63) Boige, <i>et al.</i> (2016)(69)		
		AG was observed in individuals with fluoropyrimidine toxicity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Gross, <i>et al.</i> (2003)(94) Lazar, <i>et al.</i> (2004)(95) van Kuilenburg, <i>et al.</i> (2010)(47)	Clinical	Weak
*5 rs1801159 c.1627A>G p.I543V	Activity	AG + GG are not associated with altered DPD activity as compared to AA	He, <i>et al.</i> (2008)(96) Offer, <i>et al.</i> (2013)(5) Sistonen, <i>et al.</i> (2014)(30) Kuilenburg, <i>et al.</i> (2016)(28)	Clinical, Ex vivo	High
		Within cell lines, the GG or the G allele are not associated with altered DPD activity as compared to AA	Offer, <i>et al.</i> (2013)(31) Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	High
		AG + GG were observed in individuals with decreased DPD activity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Gross, <i>et al.</i> (2003)(94) Ezzeldin, <i>et al.</i> (2005)(43) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Ridge, <i>et al.</i> (1998)(35) Collie-Duguid, <i>et al.</i> (2000)(49) Seck, <i>et al.</i> (2005)(85) Ezzeldin, <i>et al.</i> (2005)(43)	Clinical, Ex vivo	Weak

	Metabolism	AG + GG are associated with decreased metabolism of fluorouracil as compared to AA	Supports Statement: Statistically Significant: Zhang, <i>et al.</i> (2007)(97) Teh, <i>et al.</i> (2013)(98) Same Direction of Association: Gentile, <i>et al.</i> (2016)(57) Does Not Support Statement: Rudek, <i>et al.</i> (2013)(99)	Clinical, Ex vivo	Weak
	Efficacy	AG + GG are associated with increased overall survival time, or increased response to fluoropyrimidine treatment as compared to AA	Supports Statement: Statistically Significant: Grau, <i>et al.</i> (2008)(100) Joerger, <i>et al.</i> (2015)(51) Does Not Support Statement: McLeod, <i>et al.</i> (2010)(53)	Clinical	Weak
AG + GG are associated with decreased response to fluoropyrimidine treatment as compared to AA		Supports Statement: Statistically Significant: Zhang, <i>et al.</i> (2012)(101)	Clinical	Weak	
AG + GG are not associated with progression-free survival time as compared to AA		McLeod, <i>et al.</i> (2010)(53) Farina-Sarasqueta, <i>et al.</i> (2010)(102)	Clinical	Weak	

	Toxicity	AG + GG are associated with risk or severity of fluoropyrimidine toxicity as compared to AA	<p>Supports Statement: Statistically Significant (nausea/vomiting): Zhang, <i>et al.</i> (2007)(97)</p> <p>Statistically Significant (leukopenia): Zhang, <i>et al.</i> (2007)(97)</p> <p>Same Direction of Association: Rosmarin, <i>et al.</i> (2014)(66)</p> <p>Does Not Support Statement: Gross, <i>et al.</i> (2003)(94) Cho, <i>et al.</i> (2007)(103) Schwab, <i>et al.</i> (2008)(61) Kleibl, <i>et al.</i> (2009)(64) Amstutz, <i>et al.</i> (2009)(2) McLeod, <i>et al.</i> (2010)(53) Deenen, <i>et al.</i> (2011)(50) Zhang, <i>et al.</i> (2012)(101) Teh, <i>et al.</i> (2013)(98) Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3) Joerger, <i>et al.</i> (2015)(51) Toffoli, <i>et al.</i> (2015)(63) Boige, <i>et al.</i> (2016)(69)</p>	Clinical	Weak
		AG + GG were observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) van Kuilenburg, <i>et al.</i> (2000)(70) Lazar, <i>et al.</i> (2004)(95) Ezzeldin, <i>et al.</i> (2005)(43) Kim, <i>et al.</i> (2010)(104) van Kuilenburg, <i>et al.</i> (2010)(47) Zaanan, <i>et al.</i> (2014)(105)</p>	Clinical	Weak

			Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Collie-Duguid, <i>et al.</i> (2000)(49)		
*6 rs1801160 c.2194G>A p.V732I	Activity	AG/the A allele is associated with decreased DPD activity as compared to GG	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(5) Same Direction of Association: Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
		Within cell lines, the AA genotype or the A allele are associated with decreased DPD activity as compared to GG	Supports Statement: Statistically Significant: Kuilenburg, <i>et al.</i> (2016)(28) Does Not Support Statement: Offer, <i>et al.</i> (2013)(31)	In vitro	weak
		AA + AG were observed in individuals with decreased DPD activity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Seck, <i>et al.</i> (2005)(85)	Clinical, Ex vivo	weak
	Metabolism	AA + AG are associated with decreased metabolism of fluorouracil as compared to GG	Supports Statement: Statistically Significant: Gentile, <i>et al.</i> (2016)(57)	Ex vivo	weak

	Efficacy	AA + AG are not associated with complete remission rate, event-free survival or response to fluoropyrimidine treatment as compared to GG	Zhang, <i>et al.</i> (2012)(101) Zhao, <i>et al.</i> (2016)(52)	Clinical	weak
	Toxicity	AA + AG are associated with increased risk or severity of fluoropyrimidine toxicity as compared to GG	<p>Supports Statement: Statistically Significant (overall toxicity): Boige, <i>et al.</i> (2016)(69)</p> <p>Statistically Significant (myelosuppression): Kleibl, <i>et al.</i> (2009)(64) Boige, <i>et al.</i> (2016)(69)</p> <p>Statistically Significant (diarrhea): Deenen, <i>et al.</i> (2011)(50)</p> <p>Same Direction of Association: Does Not Support Statement: Schwab, <i>et al.</i> (2008)(61) Amstutz, <i>et al.</i> (2009)(2) Deenen, <i>et al.</i> (2011)(50) Zhang, <i>et al.</i> (2012)(101) Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3) Toffoli, <i>et al.</i> (2015)(63) Zhao, <i>et al.</i> (2016)(52)</p>	Clinical	weak
		AA + AG were observed in individuals with fluoropyrimidine toxicity	<p>Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) van Kuilenburg, <i>et al.</i> (2000)(70) Thomas, <i>et al.</i> (2016)(48)</p>	Clinical	weak

			Del Re, <i>et al.</i> (2015)(106) Does Not Support Statement: Thomas, <i>et al.</i> (2016)(48)		
*9A rs1801265 c.85T>C p.C29R	Activity	The CC + CT genotypes are associated with increased DPD activity as compared to TT	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(5) Sistonen, <i>et al.</i> (2014)(30) Does Not Support Statement: He, <i>et al.</i> (2008)(96) Kuilenburg, <i>et al.</i> (2016)(28)	Clinical, Ex vivo	weak
		Within cell lines, CC is associated with increased DPD activity as compared to TT	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(31)	In vitro	weak
		Within cell lines, the C allele is associated with decreased DPD activity as compared to TT	Supports Statement: Statistically Significant: Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	weak
		CC + CT were observed in individuals with decreased DPD activity	Supports Statement: Vreken, <i>et al.</i> (1997)(33) Van Kuilenburg, <i>et al.</i> (1999)(36) Van Kuilenburg, <i>et al.</i> (1999)(107) Collie-Duguid, <i>et al.</i> (2000)(49) van Kuilenburg, <i>et al.</i> (2002)(40) Gross, <i>et al.</i> (2003)(94) Ezzeldin, <i>et al.</i> (2005)(43) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Johnson, <i>et al.</i> (2002)(38)	Clinical, Ex vivo	weak

			Gross, <i>et al.</i> (2003)(94) Seck, <i>et al.</i> (2005)(85) Ezzeldin, <i>et al.</i> (2005)(43)		
	Metabolism	CC is associated with decreased metabolism of fluorouracil as compared to CT + TT	Supports Statement: Gentile, <i>et al.</i> (2016)(57) Does Not Support Statement: Boisdron-Celle, <i>et al.</i> (2007)(55) Zhang, <i>et al.</i> (2007)(97)	Clinical, Ex vivo	weak
	Efficacy	CC + CT are associated with decreased event-free survival time and decreased response to fluorouracil treatment as compared to TT	Supports Statement: Statistically Significant: Zhao, <i>et al.</i> (2016)(52)	Clinical	weak
		CC + CT is not associated with overall survival, progression-free survival or response to fluoropyrimidine treatment as compared to TT	Grau, <i>et al.</i> (2008)(100) McLeod, <i>et al.</i> (2010)(53) Joerger, <i>et al.</i> (2015)(51)	Clinical	moderate

	Toxicity	CC are associated with risk or severity of fluoropyrimidine toxicity as compared to TT	<p>Supports Statement: <i>Statistically Significant (nausea/vomiting):</i> Zhang, <i>et al.</i> (2007)(97)</p> <p><i>Statistically Significant (hand-foot syndrome):</i> Joerger, <i>et al.</i> (2015)(51)</p> <p><i>Statistically Significant (diarrhea):</i> Joerger, <i>et al.</i> (2015)(51)</p> <p><i>Statistically Significant (infection):</i> Zhao, <i>et al.</i> (2016)(52)</p> <p><i>Statistically Significant (nephrotoxicity):</i> Zhao, <i>et al.</i> (2016)(52)</p> <p><i>Statistically Significant (hepatotoxicity):</i> Zhao, <i>et al.</i> (2016)(52)</p> <p><i>Same Direction of Association (overall toxicity):</i> Froehlich, <i>et al.</i> (2015)(3)</p> <p>Does Not Support Statement: Gross, <i>et al.</i> (2003)(94) Boisdron-Celle, <i>et al.</i> (2007)(55) Morel, <i>et al.</i>(2006)(73) Schwab, <i>et al.</i> (2008)(61) Amstutz, <i>et al.</i> (2009)(2) McLeod, <i>et al.</i> (2010)(53) Deenen, <i>et al.</i> (2011)(50) Dhawan, <i>et al.</i> (2013)(68) Rosmarin, <i>et al.</i> (2014)(66)</p>	Clinical	weak
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			Rosmarin, <i>et al.</i> (2015)(9) Boige, <i>et al.</i> (2016)(69)		
		CC + CT are associated with decreased risk of gastrointestinal toxicity as compared to TT	Supports Statement: Statistically Significant: Kleibl, <i>et al.</i> (2009)(64)	Clinical	weak
		CC + CT were observed in individuals with fluoropyrimidine toxicity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) van Kuilenburg, <i>et al.</i> (2000)(70) Lazar, <i>et al.</i> (2004)(95) Kim, <i>et al.</i> (2010)(104) van Kuilenburg, <i>et al.</i> (2010)(47) Kristensen, <i>et al.</i> (2010)(65) Zaanan, <i>et al.</i> (2014)(105) Saif, <i>et al.</i> (2014)(6) Baskin, <i>et al.</i> (2015)(108) Thomas, <i>et al.</i> (2016)(48) Del Re, <i>et al.</i> (2015)(106) Does Not Support Statement: Kristensen, <i>et al.</i> (2010)(65) Thomas, <i>et al.</i> (2016)(48)	Clinical	weak

rs2297595 c.496A>G p.M166V	Activity	The AG + GG genotypes are not associated with altered DPD activity as compared to the AA genotype	Seck, <i>et al.</i> (2005)(85) Offer, <i>et al.</i> (2013)(5) Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
		Within cell lines, the G allele is associated with decreased DPD activity as compared to the AA genotype	Supports Statement: Statistically Significant: Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	weak
		Within cell lines, the G allele is associated with increased DPD activity as compared to the A allele	Supports Statement: Statistically Significant : Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The AG genotype was observed in individuals with decreased DPD activity	Supports Statement: Gross, <i>et al.</i> (2003)(94) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Johnson, <i>et al.</i> (2002)(38)	Clinical, Ex vivo	weak
	Metabolism	The AG + GG genotypes are associated with decreased metabolism of fluorouracil as compared to the AA genotype	Supports Statement: Statistically Significant: Gentile, <i>et al.</i> (2016)(57)	Ex vivo	weak

	Efficacy	The AG genotype is not associated with response to fluoropyrimidine treatment as compared to the AA genotype	Zhang, <i>et al.</i> (2012)(101)	Clinical	weak
	Toxicity	The AG + GG genotypes are associated with risk or severity of fluoropyrimidine toxicity as compared to the AA genotype	<p>Supports Statement: Statistically Significant (overall toxicity): Gross, <i>et al.</i> (2008)(77) Falvella, <i>et al.</i> (2015)(90)</p> <p>Statistically Significant (diarrhea): Deenen, <i>et al.</i> (2011)(50)</p> <p>Statistically Significant (hand-foot syndrome): Deenen, <i>et al.</i> (2011)(50)</p> <p>Same Direction of Association: Deenen, <i>et al.</i> (2011)(50)</p> <p>Does Not Support Statement for overall toxicity: Schwab, <i>et al.</i> (2008)(61) Amstutz, <i>et al.</i> (2009)(2) Zhang, <i>et al.</i> (2012)(101) Loganayagam, <i>et al.</i> (2013)(13) Rosmarin, <i>et al.</i> (2014)(66) Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3) Toffoli, <i>et al.</i> (2015)(63) Boige, <i>et al.</i> (2016)(69)</p>	Clinical	weak

		The AG + GG genotypes are associated with a decreased risk of neutropenia as compared to the AA genotype	Supports Statement: Statistically Significant: Kleibl, <i>et al.</i> (2009)(64)	Clinical	weak
		The AG genotype/the G allele was observed in individuals with fluoropyrimidine toxicity	Supports Statement: van Kuilenburg, <i>et al.</i> (2000)(70) Gross, <i>et al.</i> (2003)(94) van Kuilenburg, <i>et al.</i> (2010)(47) Kristensen, <i>et al.</i> (2010)(65) Thomas, <i>et al.</i> (2016)(48) Does Not Support Statement: Kristensen, <i>et al.</i> (2010)(65) Thomas, <i>et al.</i> (2016)(48)	Clinical	weak
rs115232898 c.557A>G p.Y186C	Activity	The AG genotype is associated with decreased DPD activity as compared to the AA genotype	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(5)	Ex vivo	Moderate
		Within cell lines, the GG genotype/the G allele is associated with decreased DPD activity as compared to the AA genotype	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(109) Offer, <i>et al.</i> (2014)(86)	In vitro	Moderate
		The AG genotype/the G allele was observed in individuals with decreased DPD activity	Supports Statement: Ezzeldin, <i>et al.</i> (2005)(43) Zaanan, <i>et al.</i> (2014)(105)	Clinical, Ex vivo	Moderate

	Toxicity	The AG genotype was observed in individuals with fluoropyrimidine toxicity	Supports Statement: Zaanan, <i>et al.</i> (2014)(105) Saif, <i>et al.</i> (2014)(6)	Clinical	Weak
rs61622928 c.1218G>A p.M406I	Activity	The AG genotype/the A allele is not associated with altered DPD activity as compared to the GG genotype	Offer, <i>et al.</i> (2013)(5) Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
		Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele	Offer, <i>et al.</i> (2014)(86) Kuilenburg, <i>et al.</i> (2016)(28)	In vitro	weak
		The AG genotype/the A allele was observed in an individual with decreased DPD activity	Supports Statement: Ezzeldin, <i>et al.</i> (2005)(43) Thomas, <i>et al.</i> (2016)(48)	Clinical, Ex vivo	weak
rs17376848 c.1896T>C p.F632F	Activity	The CC + CT genotypes are not associated with altered DPD activity as compared to the TT genotype	He, <i>et al.</i> (2008)(96) Offer, <i>et al.</i> (2013)(5)	Clinical, Ex vivo	weak
		The CT genotype/the C allele were observed in individuals with decreased DPD activity	Supports Statement: Collie-Duguid, <i>et al.</i> (2000)(49) Ezzeldin, <i>et al.</i> (2005)(43) Does Not Support Statement: Collie-Duguid, <i>et al.</i> (2000)(49)	Ex vivo	weak

	Metabolism	The CC + CT genotypes are associated with decreased metabolism of fluorouracil as compared to the TT genotype	Supports Statement: <i>Statistically Significant:</i> Teh, <i>et al.</i> (2013)(98)	Clinical	weak
	Toxicity	The CT genotype/the C allele is associated with risk or severity of fluoropyrimidine toxicity as compared to the TT genotype	Supports Statement: <i>Statistically Significant (overall toxicity):</i> Kristensen, <i>et al.</i> (2010)(65) Falvella, <i>et al.</i> (2015)(90) <i>Statistically Significant (neutropenia):</i> Teh, <i>et al.</i> (2013)(98) <i>Statistically Significant (stomatitis):</i> Joerger, <i>et al.</i> (2015)(51) Does Not Support Statement: Schwab, <i>et al.</i> (2008)(61) Kleibl, <i>et al.</i> (2009)(64) Amstutz, <i>et al.</i> (2009)(2) Deenen, <i>et al.</i> (2011)(50) Froehlich, <i>et al.</i> (2015)(3) Toffoli, <i>et al.</i> (2015)(63) Boige, <i>et al.</i> (2016)(69)	Clinical	weak
		The CT genotype was observed in individuals with fluoropyrimidine toxicity	Supports Statement: Gross, <i>et al.</i> (2003)(94)	Clinical	weak

<p>*2B</p> <p>rs1801159 + rs3918290</p> <p>1627A>G (I543V) + 1905+1G>A</p>	Activity	The *2B/*4 genotype was observed in an individual with decreased DPD activity	Supports Statement: Ridge, <i>et al.</i> (1998)(35)	Ex vivo	weak
	Toxicity	The *2B/*4 genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Ridge, <i>et al.</i> (1998)(35)	Clinical	weak
<p>*3</p> <p>rs72549303</p> <p>c.1898delC</p> <p>p.P633Qfs</p>	Activity	Within cell lines, the del allele is associated with decreased DPD activity as compared the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The C/del + del/del genotypes were observed in individuals with decreased DPD activity	Supports Statement: Vreken, <i>et al.</i> (1997)(110) Vreken, <i>et al.</i> (1997)(33) Van Kuilenburg, <i>et al.</i> (1999)(36)	Clinical, Ex vivo	weak
<p>*7</p> <p>rs72549309</p> <p>c.295_298delTCAT</p> <p>p.F100Sfs</p>	Activity	Within cell lines, the del allele is associated with decreased DPD activity as compared to the TCAT allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The del/del genotype was observed in individuals with DPYD deficiency	Supports Statement: Van Kuilenburg, <i>et al.</i> (1999)(36)	Clinical	weak

<p>*8</p> <p>rs1801266</p> <p>c.703C>T</p> <p>p.R235W</p>	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The T allele was observed in individuals with decreased DPD activity	Supports Statement: Vreken, <i>et al.</i> (1997)(110) Vreken, <i>et al.</i> (1997)(33) Van Kuilenburg, <i>et al.</i> (1999)(36)	Clinical, Ex vivo	weak
	Toxicity	The T allele was observed in an individual without fluoropyrimidine toxicity	Supports Statement: Kristensen, <i>et al.</i> (2010)(65)	Clinical	weak
<p>*9B</p> <p>rs1801267 + rs1801265</p> <p>c.2657G>A + c.85T>C</p> <p>p.R886H + p.C29R</p>	Activity	*9B/*9B/the *9B allele was observed in individuals with decreased DPD activity	Supports Statement: Vreken, <i>et al.</i> (1997)(110) Vreken, <i>et al.</i> (1997)(33) Van Kuilenburg, <i>et al.</i> (1999)(36)	Clinical, Ex vivo	weak
		Within cell lines, the A allele of the rs1801267 variant (part of *9B) is not associated with altered DPD activity as compared to the G allele	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
	Toxicity	The A allele of the rs1801267 variant (part of *9B) is not associated with risk of fluoropyrimidine toxicity as compared to the G allele	Boige, <i>et al.</i> (2016)(69)	Clinical	weak

*10 rs1801268 c.2983G>T p.V995F	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the G allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The TT genotype was observed in an individual with decreased DPD activity	Supports Statement: Van Kuilenburg, <i>et al.</i> (1999) (36)	Clinical	weak
*11 rs72549306 c.1003G>T p.V335L	Activity	The T allele was observed in individuals with decreased DPD activity	Supports Statement: Kouwaki, <i>et al.</i> (1998)(111)	Ex vivo	weak
		The T allele was observed to result in decreased DPD activity in <i>E.coli</i> lysates	Supports Statement: Kouwaki, <i>et al.</i> (1998)(111)	In vitro	weak
		Within cell lines, the T allele is not associated with altered DPD activity as compared to the G allele	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
	Toxicity	The T allele was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Kouwaki, <i>et al.</i> (1998)(111)	Clinical	weak
*12	Activity	The *12 allele was observed in individuals with decreased DPD activity		Ex vivo	weak

rs80081766 + rs78060119 c.62G>A + c.1156G>T p.R21Q + p.E386X		The T allele of the rs78060119 variant (part of *12) was observed to result in undetectable DPD activity in <i>E.coli</i> lysates	Supports Statement: Kouwaki, <i>et al.</i> (1998)(111)	In vitro	weak
		The A allele of the rs80081766 variant (part of *12) was not observed to result in altered DPD activity in <i>E.coli</i> lysates	Kouwaki, <i>et al.</i> (1998)(111)	In vitro	weak
		Within cell lines, the T allele of the rs78060119 variant (part of *12) is associated with decreased DPD activity as compared to the G allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		Within cell lines, the A allele of the rs80081766 variant (part of *12) is not associated with altered DPD activity as compared to the G allele	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
	Toxicity	The *12 allele was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Kouwaki, <i>et al.</i> (1998)(111)	Clinical	weak

		The GG genotype of the rs78060119 variant (part of *12) is not associated with risk or severity of fluoropyrimidine toxicity as compared to the TT or GT genotypes	Zhao, <i>et al.</i> (2016)(52)	Clinical	weak
rs111858276 c.1484A>G p.D495G	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs112766203 c.2279C>T p.T760I	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs114096998 c.3067C>A p.P1023T	Activity	Within cell lines, the A allele is associated with increased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs115632870 c.151-69G>A	Activity	The AG genotype is associated with decreased DPD activity as compared to the GG genotype	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak
rs12022243 1906-14763G>A	Toxicity	The A allele is associated with increased severity of fluoropyrimidine toxicity as compared to the G allele	Supports Statement: Statistically Significant: Rosmarin, <i>et al.</i> (2015)(9)	Clinical	weak
rs12132152 g.97523004G>A ^e	Toxicity	The A allele is associated with increased severity of fluoropyrimidine toxicity as compared to the G allele	Supports Statement: Statistically Significant: Rosmarin, <i>et al.</i> (2015)(9)	Clinical	weak
rs76387818 g.97539400G>A ^e	Toxicity	The A allele is associated with increased severity of fluoropyrimidine toxicity as compared to the G allele	Supports Statement: Statistically Significant: Rosmarin, <i>et al.</i> (2015)(9)	Clinical	weak

rs7548189 c.1906-19696G>T	Toxicity	The T allele is associated with increased severity of fluoropyrimidine toxicity as compared to the G allele	Supports Statement: <i>Same Direction of Association:</i> Rosmarin, <i>et al.</i> (2015)(9)	Clinical	weak
rs137999090 c.2021G>A p.G674D	Activity	Within cell lines, the A allele is associated with decreased DPD activity as compared to the G allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs138616379 c.1775G>A p.R592Q	Activity	Within cell lines, the A allele is associated with decreased DPD activity as compared to the G allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs141044036 c.2872A>G p.K958E	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs143154602 c.1057C>T p.R353C	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs143986398 c.274C>G p.P92A	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs145773863 c.1777G>A p.G593R	Activity	Within cell lines, the A allele is associated with decreased DPD activity as compared to the G allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs146356975 c.868A>G p.K290E	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: <i>Statistically Significant:</i> Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs147601618 c.1796T>C p.M599T	Toxicity	The CT genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Ofverholm, <i>et al.</i> (2010)(112)	Clinical	weak
	Activity	Within cell lines, the C allele is not associated with DPD activity as compared to the T allele	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs183105782 c.910T>C p.Y304H	Activity	Within cell lines, the C allele is associated with decreased DPD activity as compared to the T allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs183385770 c.1024G>A p.D342N	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs186169810 c.1314T>G p.F438L	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the T allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs188052243 c.2678A>G p.N893S	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs190577302 c.1054C>G p.L352V	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs200687447 c.2482G>A p.E828K	Activity	Within cell lines, the A allele is associated with increased DPD activity as compared to the G allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs367619008 187A>G p.K63E	Toxicity	The AG genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Kleibl, <i>et al.</i> (2009)(64)	Clinical	weak
rs376073289 c.623G>A p.R208Q	Toxicity	The AG genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Thomas, <i>et al.</i> (2016)(48)	Clinical	weak
		The A allele is not associated with risk of fluoropyrimidine toxicity	Schwab, <i>et al.</i> (2008)(61)	Clinical	weak
rs45589337 c.775A>G p.K259E	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the A allele	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

		The G allele is not associated with altered DPD activity as compared to the AA genotype	Sistonen, <i>et al.</i> (2014)(30)	Clinical	weak
		The AG genotype was observed in an individual without altered DPD activity	Supports Statement: Gross, <i>et al.</i> (2003)(94)	Ex vivo	weak
	Toxicity	The AG genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Gross, <i>et al.</i> (2003)(94)	Clinical	weak
		The AG genotype/the G allele is not associated with risk or severity of fluoropyrimidine toxicity as compared to the AA genotype	Schwab, <i>et al.</i> (2008)(61) Rosmarin, <i>et al.</i> (2015)(9) Froehlich, <i>et al.</i> (2015)(3)	Clinical	weak

rs55674432 c.2639G>T p.G880V	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the G allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs56293913 c.1129-15T>C	Activity	The CC + CT genotypes are not associated with altered DPD activity as compared to the TT genotype	Offer, <i>et al.</i> (2013)(5) Sistonen, <i>et al.</i> (2014)(30)	Clinical, Ex vivo	weak
	Toxicity	The CC + CT genotypes are associated with increased severity of fluoropyrimidine toxicity as compared to the TT genotype	Supports Statement: Statistically Significant: Gross, <i>et al.</i> (2008)(77) Same Direction of Association: Amstutz, <i>et al.</i> (2009)(2) Deenen, <i>et al.</i> (2011)(50)	Clinical	weak
rs568132506 c.257C>T p.P86L	Activity	The CT + TT genotypes were observed in individuals with decreased DPD activity	Supports Statement: van Kuilenburg, <i>et al.</i> (2002)(40) Thomas, <i>et al.</i> (2016)(48)	Clinical, Ex vivo	weak

	Toxicity	The CT genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Thomas, <i>et al.</i> (2016)(48)	Clinical	weak
rs59086055 c.1774C>T p.R592W	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs60139309 c.2582A>G p.K861R	Activity	Within cell lines, the G allele is associated with increased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs61757362 c.2948C>T p.T983I	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs72547601 c.2933A>G p.H978R	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The GG genotype was observed in an individual with decreased DPD activity	Supports Statement: van Kuilenburg, <i>et al.</i> (2002)(40)	Ex vivo	weak
rs72549304 c.1475C>T p.S492L	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The TT genotype was observed in an individual with decreased DPD activity	Supports Statement: van Kuilenburg, <i>et al.</i> (2002)(40)	Ex vivo	weak
rs72549305 c.1108A>G p.I370V	Activity	Within cell lines, the G allele is not associated with DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The GG genotype was observed in an individual with decreased DPD activity	Supports Statement: van Kuilenburg, <i>et al.</i> (2002)(40)	Ex vivo	weak

rs72549307 c.632A>G p.Y211C	Activity	Within cell lines, the G allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The GG genotype was observed in an individual with decreased DPD activity	Supports Statement: (van Kuilenburg, <i>et al.</i> (2002)(40)	Ex vivo	weak
	Toxicity	The G allele is not associated with risk or severity of fluoropyrimidine toxicity	Froehlich, <i>et al.</i> (2015)(3)	Clinical	weak
rs72549308 c.601A>C p.S201R	Activity	Within cell lines, the C allele is associated with decreased DPD activity as compared to the A allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs72549310 c.61C>T p.R21X	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs72728438 c.1974+75A>G	Activity	The AG genotype is associated with decreased DPD activity as compared to the AA genotype	Supports Statement: Statistically Significant: Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak

rs777425216 c.1651G>A p.A551T	Toxicity	The AG genotype was observed in an individual with fluoropyrimidine toxicity	Supports Statement: Rosmarin, <i>et al.</i> (2015)(9)	Clinical	weak
rs150036960 c.46C>G p.L16V	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs150385342 c.313G>A p.A105T	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs141462178 c.343A>G p.M115V	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs200562975 c.451A>G p.N151D	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs139834141 c.498G>A p.M166I	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs150437414 c.929T>C p.L310S	Activity	Within cell lines, the C allele is not associated with altered DPD activity as compared to the T allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs145112791 c.934C>T p.L312F	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs201018345 c.967G>A p.A323T	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(574)	In vitro	weak
rs143815742 c.1181G>T p.R394L	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs140602333 c.1180C>T p.R394W	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs200064537 c.1260T>A p.N420K	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the T allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs764666241 c.1278G>T p.M426I	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs142512579 c.1294G>A p.D432N	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs72975710 c.1349C>T p.A450V	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs144395748 c.1358C>G p.P453R	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
		The GG genotype is not associated with altered DPD activity as compared to the CG genotype.	Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak
rs199549923 c.1403C>A p.T468N	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs138391898 c.1519G>A p.V507I	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs148994843 c.1543G>A p.V515I	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs190951787 c.1577C>G p.T526S	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs142619737 c.1615G>A p.G539R	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs201615754 c.1682G>T p.R561L	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs3918289 c.1905C>G p.N635K	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs55971861 c.1906A>C p.I636L	Activity	Within cell lines, the C allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs138545885 c.1990G>T p.A664S	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs145548112 c.2161G>A p.A721T	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs146529561 c.2186C>T p.A729V	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs60511679 c.2195T>G p.V732G	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the T allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs56005131 c.2303C>A p.T768K	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs199634007 c.2336C>A p.T779N	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs201035051 c.2623A>C p.K875Q	Activity	Within cell lines, the C allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs147545709 c.2656C>T p.R886C	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs145529148 c.2915A>G p.Q972R	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs72547602 c.2921A>T p.D974V	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the A allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak

rs139459586 c.2978T>G p.L993R	Activity	Within cell lines, the G allele is not associated with altered DPD activity as compared to the T allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs202144771 c.2977C>T p.L993F	Activity	Within cell lines, the T allele is not associated with altered DPD activity as compared to the C allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs140114515 c.3049G>A p.V1017I	Activity	Within cell lines, the A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs148799944 c.3061G>C p.V1021L	Activity	Within cell lines, the C allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2014)(86)	In vitro	weak
rs6670886 c.525G>A p.S175S	Activity	The A allele is not associated with altered DPD activity as compared to the G allele.	Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak

rs3790387 c.763-118A>G	Activity	The AG + GG genotypes are not associated with altered DPD activity as compared to the AA genotype.	Offer, <i>et al.</i> (2013)(5) Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
		The G allele is not associated with altered DPD activity as compared to the A allele.	Sistonen, <i>et al.</i> (2014)(30)	Clinical	weak
rs112550271 c.850+41T>C	Activity	The CT genotype is not associated with altered DPD activity as compared to the TT genotype.	Offer, <i>et al.</i> (2013)(5) Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
rs2811202 c.958+134T>G	Activity	The GG + GT genotypes are not associated with altered DPD activity as compared to the TT genotype.	Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak
rs61789183 c.1340-106T>A	Activity	The AA + AT genotypes are not associated with altered DPD activity as compared to the TT genotype.	Offer, <i>et al.</i> (2013)(5) Kuilenburg, <i>et al.</i> (2016)(28)	Ex vivo	weak
rs57918000 c.1371C>T p.N457N	Activity	The CT genotype is not associated with altered DPD activity as compared to the CC genotype.	Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak

rs2786783 c.1740+39C>T	Activity	The CT + TT genotypes are not associated with altered DPD activity as compared to the CC genotype.	Offer, <i>et al.</i> (2013)(5) Sistonen, <i>et al.</i> (2014)(30)	Ex vivo, Clinical	weak
rs2811178 1740+40A>G	Activity	The AG + GG genotypes are not associated with altered DPD activity as compared to the AA genotype.	Offer, <i>et al.</i> (2013)(5) Sistonen, <i>et al.</i> (2014)(30)	Ex vivo, Clinical	weak
rs12137711 c.2300-39G>A	Activity	The AG genotype is not associated with altered DPD activity as compared to the GG genotype.	Offer, <i>et al.</i> (2013)(5)	Ex vivo	weak
rs41309171 c.234-123G>C	Activity	The CG genotype is not associated with altered DPD activity as compared to the GG genotype.	Sistonen, <i>et al.</i> (2014)(30)	Clinical	weak
rs138924556 c.850+91C>T	Activity	The CT genotype is not associated with altered DPD activity as compared to the CC genotype.	Sistonen, <i>et al.</i> (2014)(30)	Clinical	weak

rs368600943 c.1129-28G>T	Activity	The GT genotype is not associated with altered DPD activity as compared to the GG genotype.	Sistonen, <i>et al.</i> (2014)(30)	Clinical	weak
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^aNucleotide changes according to reference sequence NM_000110.3 unless otherwise specified

^bProtein changes according to reference sequence NP_000101.2

^cRating Scheme for Quality of Evidence as per (16)

^dSome of the small case series, although not strong individually, collectively do support a strong recommendation.

^eNucleotide changes according to NC_000001.10

^fLikely HapB3 causal variant. Proxy SNPs are c.1236G>A (rs56038477, E412E), c.483+18G>A (rs56276561) and c.959-51T>G (rs115349832). c.680+139G>A (rs6668296) is not exclusive to HapB3 and therefore not a suitable proxy.

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