Supplemental Material

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

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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) 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 vitr*o 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 (*NLGN1*), rs2465403 (*COLEC10*), rs10876844 (*OR10AE3P*, *PSMB2*P), 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

DPYD ***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, *et al.* (1996)(27) Kuilenburg, *et al*. (2016)(28) Nie, *et al*. (2017)(29) ***Same Direction of Association:*** Sistonen, *et al*. (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, *et al.* (2013)(31)	In vitro	**High**
		AA + AG were observed in individuals with decreased DPD activity	**Supports Statement:** Holopainen, *et al.* (1997)(32) Vreken, *et al.* (1997)(33) Van Kuilenburg, *et al.* (1997)(34) Ridge, *et al.* (1998)(35) Van Kuilenburg, *et al.* (1999)(36) van Kuilenburg, *et al.* (2001)(37) Johnson, *et al.* (2002)(38) Maring, *et al.* (2002)(39) van Kuilenburg, *et al.* (2002)(40) Van Kuilenburg, *et al.* (2002)(41) Al-Sanna'a, *et al.* (2005)(42)	Clinical, Ex vivo	**High**

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

		Individuals with AG were observed to have decreased metabolism of fluorouracil	**Supports Statement:** Maring, *et al.* (2002)(58) Joerger, *et al.* (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, *et al.* (2002)(59) Salgueiro, *et al.* (2004)(60) Boisdron-Celle, *et al.* (2007)(55) Schwab, *et al.* (2008)(61) Deenen, *et al.* (2011)(50) Lee, *et al.* (2014)(62) Toffoli, *et al.* (2015)(63) ***Statistically Significant (myelosuppression):*** Schwab, *et al.* (2008)(61) Kleibl, *et al.* (2009)(64) Kristensen, *et al.* (2010)(65) Rosmarin, *et al.* (2014)(66) Cai, *et al.* (2014)(54) ***Statistically Significant (hand-foot syndrome):*** Cai, *et al.* (2014)(54) ***Statistically Significant (diarrhea):*** Deenen, *et al.* (2011)(50) Cai, *et al.* (2014)(54) ***Statistically Significant (mucositis):*** Schwab, *et al.* (2008)(61)	Clinical	**High**

			Kleibl, *et al.* (2009)(64) ***Statistically Significant (hepatotoxicity):*** Zhao, *et al.* (2016)(52) ***Statistically Significant (infection):*** Zhao, *et al.* (2016)(52) ***Same Direction of Association (overall toxicity)*:** Braun, *et al.* (2009)(67) Dhawan, *et al.* (2013)(68) Rosmarin, *et al.* (2014)(66) Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (2015)(3) Boige, *et al.* (2016)(69) ***Same Direction of Association (neutropenia):*** McLeod, *et al.* (2010)(53) **Does Not Support Statement:** Amstutz, *et al.* (2009)(2) McLeod, *et al.* (2010)(53)		

		AA + AG were observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Wei, *et al.* (1996)(27) Van Kuilenburg, *et al.*(1997)(34) van Kuilenburg, *et al.* (2000)(70) van Kuilenburg, *et al.* (2001)(37) Raida, *et al.* (2001)(71) Johnson, *et al.* (2002)(38) Maring, et al. (2002)(58) Van Kuilenburg, *et al.* (2002)(41) Steiner, *et al.* (2005)(72) Ezzeldin, *et al.* (2005)(43) Largillier, *et al.* (2006)(44) Morel, *et al.* (2006)(73) Saif, *et al.* (2007)(74) Salgado, *et al.* (2007)(75) Magne, *et al.* (2007)(45) Sulzyc-Bielicka, *et al.(*2008)(76) Gross, *et al.* (2008)(77) Loganayagam, *et al.* (2010)(46) Boige, *et al.* (2010)(78) Ceric, *et al.* (2010)(79) van Kuilenburg, *et al.* (2010)(47) Savva-Bordalo, *et al.* (2010)(80) Cellier, *et al.* (2011)(147) Loganayagam, *et al.* (2013)(13) Suarez Martinez-Falero, *et al.* (2014)(81) Joerger, et al. (2015)(51) Thomas, *et al.* (2016)(48) Roberto, *et al.* (2017)(82)	Clinical	**High**

*13 rs55886062 c.1679T>G p.I560S	Activity	GT is associated with decreased DPD activity as compared to TT	**Supports Statement: *Statistically Significant:*** Offer, *et al.(*2013)(5) Nie, *et al.* (2017)(29) ***Same Direction of Association:*** Sistonen, *et al.* (2014)(30)	Clinical, Ex vivo	**Moderate**
		Within cell lines, GG is associated with decreased DPD activity was compared to TT	**Supports Statement: *Statistically Significant:*** Offer, *et al.* (2013)(31)	In vitro	**High**
		GT was observed in individuals with decreased DPD activity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Johnson, *et al.* (2002)(38) van Kuilenburg, *et al*. (2002)(40) Ezzeldin, *et al.* (2005)(43) Thomas, *et al.* (2016)(48)	Clinical, Ex vivo	**High**
	Toxicity	GT is associated with increased risk or severity of fluoropyrimidine toxicity as compared to TT	**Supports Statement: *Same Direction of Association (overall toxicity):*** Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (2015)(3) Lee, *et al.* (2014)(62) Toffoli, *et al.* (2015)(63) **Does Not Support Statement:** Amstutz, *et al.* (2009)(2) Deenen, *et al.* (2011)(50) Boige, *et al.* (2016)(69)	Clinical	**High**
		GT was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Johnson, *et al.* (2002)(38) Ezzeldin, *et al.* (2005)(43)	Clinical	**High**

			Morel, *et al.* (2006)(73) Loganayagam, *et al*. (2010)(46) Cellier, *et al.* (2011)(83) Loganayagam, *et al.* (2013)(13) Dhelens, *et al.* (2016)(84) Thomas, *et al.* (2016)(48)		
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, *et al.* (2005)(85) ***Same Direction of Association:*** Sistonen, *et al*. (2014)(30) Kuilenburg, *et al.* (2016)(28) Nie, *et al.* (2017)(29) **Does Not Support Statement:** Offer, *et al.* (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, *et al.* (2014)(86) Kuilenburg, *et al.* (2016)(28)	In vitro	**High**
		The AT genotype/the T allele was observed in individuals with decreased DPD activity	**Supports Statement:** van Kuilenburg, *et al.* (2002)((40) Loganayagam, *et al.* (2010)(46) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Loganayagam, *et al.* (2010)(46)	Clinical, Ex vivo	**Moderate**

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

			***Same Direction of Association (overall toxicity)*:** Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (2015)(3)		
		The AT genotype/the T allele was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** van Kuilenburg, *et al.* (2000)(70) Morel, *et al.* (2006)(73) Gross, *et al.* (2008)(77) Loganayagam, *et al.* (2010)(46) Obi, et al. (2011)(87) Cellier, *et al.* (2011)(83) Loganayagam, *et al.* (2013)(13) Thomas, *et al.* (2016)(48) Kuilenburg, *et al.* (2016)(28) **Does Not Support Statement:** Kristensen, *et al.* (2010)(65)	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	**Supports Statement: *Statistically Significant:*** Sistonen, *et al.* (2014)(30) Nie, et al. (2017)(29) ***Same Direction of Association:*** Offer, *et al.* (2013)(5)	Ex vivo, Clinical	**Moderate**
		HapB3 was observed in individuals with decreased DPD activity	**Supports Statement:** van Kuilenburg, *et al.* (2010)(47) Meulendijks, *et al.* (2016)(88) **Does Not Support Statement:** Seck, *et al.* (2005)(85)	Ex vivo	**Moderate**

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

			Does Not Support Statement: Meulendijks, *et al.* (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, *et al.* (2006)(73) Saif, *et al.* (2013)(91) ***Statistically Significant (gastrointestinal events):*** Capitain, *et al.* (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, *et. al* (2013)(93) Froehlich, *et al* (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, *et al.* (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: *Statistically Significant:*** Sistonen, *et al.* (2014)(30) Kuilenburg, *et al.* (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: *Statistically Significant:*** Seck, *et al.* (2005)(85) ***Same Direction of Association:*** Sistonen, *et al.* (2014)(30) Kuilenburg, *et al*. (2016)(28) **Does Not Support Statement:** Offer, *et al* (2013)(5)	Clinical, Ex vivo	**Weak**

		AG was observed in individuals with decreased DPD activity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Gross, *et al.* (2003)(94) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Ridge, *et al.* (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, *et al.* (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, *et al*. (2013)(31)	In vitro	**Weak**
	Metabolism	AG is not associated with altered fluorouracil metabolism as compared to GG	Gentile, *et al.* (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, *et al.* (2015)(3) Loganayagam, *et al.* (2013)(13) Rosmarin, *et al.* (2014)(66) Rosmarin, *et al.* (2015)(9) **Does Not Support Statement:** Schwab, *et al.* (2008)(61) Kleibl, *et al.* (2009)(64) Amstutz, *et al.* (2009)(2) Deenen, *et al.* (2011)(50) Froehlich, *et al.* (2015)(3)	Clinical	**Weak**

			Toffoli, *et al.* (2015)(63) Boige, *et al.* (2016)(69)		
		AG was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Collie-Duguid, et al. (2000)(49) Gross, *et al.* (2003)(94) Lazar, *et al.* (2004)(95) van Kuilenburg, *et al.* (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, *et al.* (2008)(96) Offer, *et. al.* (2013)(5) Sistonen, *et al.* (2014)(30) Kuilenburg, *et al.* (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, *et al.* (2013)(31) Kuilenburg, *et al.* (2016)(28)	In vitro	**High**
		AG + GG were observed in individuals with decreased DPD activity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Gross, *et al.* (2003)(94) Ezzeldin, *et al.* (2005)(43) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Ridge, *et al.* (1998)(35) Collie-Duguid, *et al.* (2000)(49) Seck, *et al.* (2005)(85) Ezzeldin, *et al.* (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, *et al.* (2007)(97) Teh, *et al.* (2013)(98) ***Same Direction of Association:*** Gentile, *et al.* (2016)(57) **Does Not Support Statement:** Rudek, *et al.* (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, *et al.* (2008)(100) Joerger, *et al.* (2015)(51) **Does Not Support Statement:** McLeod, *et al.* (2010)(53)	Clinical	**Weak**
		AG + GG are associated with decreased response to fluoropyrimidine treatment as compared to AA	**Supports Statement: *Statistically Significant:*** Zhang, *et al.* (2012)(101)	Clinical	**Weak**
		AG + GG are not associated with progression-free survival time as compared to AA	McLeod, *et al.* (2010)(53) Farina-Sarasqueta, *et al.* (2010)(102)	Clinical	**Weak**

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

			Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Collie-Duguid, *et al.* (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, *et al.* (2013)(5) ***Same Direction of Association:*** Kuilenburg, *et al.* (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, *et al.* (2016)(28)**Does Not Support Statement:** Offer, *et al.* (2013)(31)	In vitro	**weak**
		AA + AG were observed in individuals with decreased DPD activity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Collie-Duguid, *et al.* (2000)(49) Seck, *et al.* (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, *et al.* (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, *et al.* (2012)(101) Zhao, *et al.* (2016)(52)	Clinical	**weak**
	Toxicity	AA + AG are associated with increased risk or severity of fluoropyrimidine toxicity as compared to GG	**Supports Statement: *Statistically Significant (overall toxicity):*** Boige, *et al.* (2016)(69) ***Statistically Significant (myelosuppression):*** Kleibl, *et al.* (2009)(64) Boige, *et al.* (2016)(69) ***Statistically Significant (diarrhea):*** Deenen, *et al.* (2011)(50) ***Same Direction of Association:*** **Does Not Support Statement:** Schwab, *et al.* (2008)(61) Amstutz, *et al.* (2009)(2) Deenen, *et al.* (2011)(50) Zhang, *et al.* (2012)(101) Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (2015)(3) Toffoli, *et al.* (2015)(63) Zhao, *et al.* (2016)(52)	Clinical	**weak**
		AA + AG were observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) van Kuilenburg, *et al.* (2000)(70) Thomas, *et al.* (2016)(48)	Clinical	**weak**

			Del Re, *et al.* (2015)(106) **Does Not Support Statement:** Thomas, *et al.* (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, *et al.* (2013)(5) Sistonen, *et al.* (2014)(30) **Does Not Support Statement:** He, *et al.* (2008)(96) Kuilenburg, *et al.* (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, *et al.* (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, *et al.* (2016)(28)	In vitro	**weak**
		CC + CT were observed in individuals with decreased DPD activity	**Supports Statement:** Vreken, *et al.* (1997)(33) Van Kuilenburg, *et al.*(1999)(36) Van Kuilenburg, *et al.* (1999)(107) Collie-Duguid, *et al.* (2000)(49) van Kuilenburg, *et al.* (2002)(40) Gross, *et al.* (2003)(94) Ezzeldin, *et al.* (2005)(43) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Collie-Duguid, *et al.* (2000)(49) Johnson, *et al.* (2002)(38)	Clinical, Ex vivo	**weak**

			Gross, *et al.* (2003)(94) Seck, *et al.* (2005)(85) Ezzeldin, *et al.* (2005)(43)		
	Metabolism	CC is associated with decreased metabolism of fluorouracil as compared to CT + TT	**Supports Statement:** Gentile, *et al.* (2016)(57) **Does Not Support Statement:** Boisdron-Celle, *et al.* (2007)(55) Zhang, *et al.* (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, *et al.* (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, *et al.* (2008)(100) McLeod, *et al.* (2010)(53) Joerger, *et al.* (2015)(51)	Clinical	**moderate**

	Toxicity	CC are associated with risk or severity of fluoropyrimidine toxicity as compared to TT	**Supports Statement: *Statistically Significant (nausea/vomiting):*** Zhang, *et al.* (2007)(97) ***Statistically Significant (hand-foot syndrome):*** Joerger, *et al.* (2015)(51) ***Statistically Significant (diarrhea):*** Joerger, *et al.* (2015)(51) ***Statistically Significant (infection):*** Zhao, *et al.* (2016)(52) ***Statistically Significant (nephrotoxicity):*** Zhao, *et al.* (2016)(52) ***Statistically Significant (hepatotoxicity):*** Zhao, *et al.* (2016)(52) ***Same Direction of Association (overall toxicity):*** Froehlich, *et al.* (2015)(3) **Does Not Support Statement:** Gross, *et al.* (2003)(94) Boisdron-Celle, *et al.* (2007)(55) Morel, *et al.(*2006)(73) Schwab, *et al.* (2008)(61) Amstutz, *et al.* (2009)(2) McLeod, *et al.* (2010)(53) Deenen, *et al.* (2011)(50) Dhawan, *et al.* (2013)(68) Rosmarin, *et al.* (2014)(66)	Clinical	**weak**

			Rosmarin, *et al.* (2015)(9) Boige, *et al.* (2016)(69)		
		CC + CT are associated with decreased risk of gastrointestinal toxicity as compared to TT	**Supports Statement: *Statistically Significant:*** Kleibl, *et al.* (2009)(64)	Clinical	**weak**
		CC + CT were observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) van Kuilenburg, *et al* (2000)(70) Lazar, *et al.* (2004)(95) Kim, *et al.* (2010)(104) van Kuilenburg, *et al*. (2010)(47) Kristensen, *et al.* (2010)(65) Zaanan, *et al.* (2014)(105) Saif, *et al.* (2014)(6) Baskin, *et al.* (2015)(108) Thomas, *et al.* (2016)(48) Del Re, *et al.* (2015)(106) **Does Not Support Statement:** Kristensen, *et al.* (2010)(65) Thomas, *et al.* (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, *et al.* (2005)(85) Offer, et al. (2013)(5) Kuilenburg, *et al.* (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, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The AG genotype was observed in individuals with decreased DPD activity	**Supports Statement:** Gross, *et al.* (2003)(94) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Johnson, *et al.* (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, *et al.* (2016)(57)	Ex vivo	**weak**

	Efficacy	The AG genotype is not associated with response to fluoropyrimidine treatment as compared to the AA genotype	Zhang, *et al.* (2012)(101)	Clinical	**weak**
	Toxicity	The AG + GG genotypes are associated with risk or severity of fluoropyrimidine toxicity as compared to the AA genotype	**Supports Statement: *Statistically Significant (overall toxicity):*** Gross, *et al.* (2008)(77) Falvella, *et al.* (2015)(90) ***Statistically Significant (diarrhea):*** Deenen, *et al.* (2011)(50) ***Statistically Significant (hand-foot syndrome):*** Deenen, *et al.* (2011)(50) ***Same Direction of Association:*** Deenen, *et al.* (2011)(50) **Does Not Support Statement for overall toxicity:** Schwab, *et al.* (2008)(61) Amstutz, *et al.* (2009)(2) Zhang, *et al.* (2012)(101) Loganayagam, *et al.* (2013)(13) Rosmarin, *et al.* (2014)(66) Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (2015)(3) Toffoli, *et al.* (2015)(63) Boige, *et al.* (2016)(69)	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, *et al.* (2009)(64)	Clinical	**weak**
		The AG genotype/the G allele was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** van Kuilenburg, *et al.* (2000)(70) Gross, *et al.* (2003)(94) van Kuilenburg, *et al.* (2010)(47) Kristensen, *et al.* (2010)(65) Thomas, *et al.* (2016)(48) **Does Not Support Statement:** Kristensen, *et al.* (2010)(65) Thomas, *et al.* (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, *et al.* (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, *et al.* (2014)(109) Offer, *et al.* (2014)(86)	In vitro	**Moderate**
		The AG genotype/the G allele was observed in individuals with decreased DPD activity	**Supports Statement:** Ezzeldin, *et al.* (2005)(43) Zaanan, *et al.* (2014)(105)	Clinical, Ex vivo	**Moderate**

	Toxicity	The AG genotype was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Zaanan, et al. (2014)(105) Saif, *et al*. (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, *et al.* (2013)(5) Kuilenburg, *et al.* (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, *et al.* (2014)(86) Kuilenburg, *et al.* (2016)(28)	In vitro	**weak**
		The AG genotype/the A allele was observed in an individual with decreased DPD activity	**Supports Statement:** Ezzeldin, *et al.* (2005)(43) Thomas, *et al.* (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, *et al.* (2008)(96) Offer, *et al.* (2013)(5)	Clinical, Ex vivo	**weak**
		The CT genotype/the C allele were observed in individuals with decreased DPD activity	**Supports Statement:** Collie-Duguid, *et al.* (2000)(49) Ezzeldin, *et al*. (2005)(43) **Does Not Support Statement:** Collie-Duguid, *et al.* (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: *Statistically Significant:*** Teh, *et al.* (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: *Statistically Significant (overall toxicity):*** Kristensen, *et al.* (2010)(65) Falvella, *et al.* (2015)(90) ***Statistically Significant (neutropenia):*** Teh, *et al.* (2013)(98) ***Statistically Significant (stomatitis):*** Joerger, *et al.* (2015)(51) **Does Not Support Statement:** Schwab, *et al.* (2008)(61) Kleibl, *et al.* (2009)(64) Amstutz, *et al.* (2009)(2) Deenen, *et al.* (2011)(50) Froehlich, *et al.* (2015)(3) Toffoli, *et al.* (2015)(63) Boige, *et al.* (2016)(69)	Clinical	**weak**
		The CT genotype was observed in individuals with fluoropyrimidine toxicity	**Supports Statement:** Gross, *et al.* (2003)(94)	Clinical	**weak**

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

*8 rs1801266 c.703C>T p.R235W	Activity	Within cell lines, the T allele is associated with decreased DPD activity as compared to the C allele	**Supports Statement: *Statistically Significant:*** Offer, *et al.* (2014)(86)	In vitro	**weak**
		The T allele was observed in individuals with decreased DPD activity	**Supports Statement:** Vreken, *et al.* (1997)(110) Vreken, *et al.* (1997)(33) Van Kuilenburg, *et al.* (1999)(36)	Clinical, Ex vivo	**weak**
	Toxicity	The T allele was observed in an individual without fluoropyrimidine toxicity	**Supports Statement:** Kristensen, *et al.* (2010)(65)	Clinical	**weak**
*9B rs1801267 + rs1801265 c.2657G>A + c.85T>C p.R886H + p.C29R	Activity	*9B/*9B/the *9B allele was observed in individuals with decreased DPD activity	**Supports Statement:** Vreken, *et al.* (1997)(110) Vreken, *et al.* (1997)(33) Van Kuilenburg, *et al.*(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, *et al.* (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, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The TT genotype was observed in an individual with decreased DPD activity	**Supports Statement:** Van Kuilenburg, *et al.* (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, *et al.* (1998)(111)	Ex vivo	**weak**
		The T allele was observed to result in decreased DPD activity in *E.coli* lysates	**Supports Statement:** Kouwaki, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
	Toxicity	The T allele was observed in an individual with fluoropyrimidine toxicity	**Supports Statement:** Kouwaki, *et al.* (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 *E.coli* lysates	**Supports Statement:** Kouwaki, *et al.* (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 *E.coli* lysates	Kouwaki, *et al*. (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, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
	Toxicity	The *12 allele was observed in an individual with fluoropyrimidine toxicity	**Supports Statement:** Kouwaki, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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: *Same Direction of Association*:** Rosmarin, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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: *Statistically Significant:*** Offer, *et al.* (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, *et al.* (2010)(112)	Clinical	**weak**
	Activity	Within cell lines, the C allele is not associated with DPD activity as compared to the T allele	Offer, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (2016)(48)	Clinical	**weak**
		The A allele is not associated with risk of fluoropyrimidine toxicity	Schwab, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**

		The G allele is not associated with altered DPD activity as compared to the AA genotype	Sistonen, *et al.* (2014)(30)	Clinical	**weak**
		The AG genotype was observed in an individual without altered DPD activity	**Supports Statement:** Gross, *et al.* (2003)(94)	Ex vivo	**weak**
	Toxicity	The AG genotype was observed in an individual with fluoropyrimidine toxicity	**Supports Statement:** Gross, *et al.* (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, *et al.* (2008)(61) Rosmarin, *et al.* (2015)(9) Froehlich, *et al.* (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, *et al.* (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, *et al.* (2013)(5) Sistonen, *et al*. (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, *et al.* (2008)(77) ***Same Direction of Association:*** Amstutz, *et al.* (2009)(2) Deenen, *et al.* (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, *et al.* (2002)(40) Thomas, *et al.* (2016)(48)	Clinical, Ex vivo	**weak**

	Toxicity	The CT genotype was observed in an individual with fluoropyrimidine toxicity	**Supports Statement:** Thomas, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The GG genotype was observed in an individual with decreased DPD activity	**Supports Statement:** van Kuilenburg, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The TT genotype was observed in an individual with decreased DPD activity	**Supports Statement:** van Kuilenburg, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The GG genotype was observed in an individual with decreased DPD activity	**Supports Statement:** van Kuilenburg, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The GG genotype was observed in an individual with decreased DPD activity	**Supports Statement:** (van Kuilenburg, *et al.* (2002)(40)	Ex vivo	**weak**
	Toxicity	The G allele is not associated with risk or severity of fluoropyrimidine toxicity	Froehlich, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al*. (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, *et al.* (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, *et al*. (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (2014)(86)	In vitro	**weak**
		The GG genotype is not associated with altered DPD activity as compared to the CG genotype.	Offer, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (2013)(5) Kuilenburg, *et al.* (2016)(28)	Ex vivo	**weak**
		The G allele is not associated with altered DPD activity as compared to the A allele.	Sistonen, *et al*. (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, *et al.* (2013)(5) Kuilenburg, *et al.* (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, *et. al.* (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, *et al.* (2013)(5) Kuilenburg, *et al.* (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, *et al.* (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, *et al.* (2013)(5) Sistonen, *et al.* (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, *et al.* (2013)(5) Sistonen, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (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, *et al.* (2014)(30)	Clinical	**weak**

[a]Nucleotide changes according to reference sequence NM_000110.3 unless otherwise specified

[b]Protein changes according to reference sequence NP_000101.2

[c]Rating Scheme for Quality of Evidence as per (16)

[d]Some of the small case series, although not strong individually, collectively do support a strong recommendation.

[e]Nucleotide changes according to NC_000001.10

[f]Likely 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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