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Fluorouracil Therapy and *DPYD* Genotype

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Introduction

Fluorouracil, or 5-flourouracil (5-FU), is a chemotherapy agent that belongs to the drug class of fluoropyrimidines. When given as an intravenous (IV) solution, 5-FU is used in the palliative management of carcinoma of many solid tumors including (but not limited to) colon, rectum, breast, esophagus, cholangiocarcinoma (bile duct cancers), stomach, and pancreas. When prescribed as a cream or solution for topical use, fluorouracil (brand names Carac, Efudex, Fluoroplex, Tolak) is used to treat multiple actinic or solar keratoses of the face and scalp. Capecitabine (brand name Xeloda or CAPE) is the oral pill form of 5-FU chemotherapy, which is used interchangeably with 5-FU IV chemotherapy. Although it is the same drug, the oral pill version has certain side effects that are more pronounced (for example, diarrhea or skin related side effects – 'hand-foot' syndrome). Given the common usage of 5-FU for a variety of malignancies and potentially fatal overdoses, an antidote has been developed—uridine triacetate—which may be useful for pharmacogenetic-related overdoses, as well.

The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), an enzyme that catalyzes the rate-limiting step in fluorouracil metabolism. Genetic variations in the *DPYD* gene can lead to enzymes with reduced or absent activity. Individuals who have at least one copy of a non-functional *DPYD* variant [for example, *DPYD*2A* (c.1905+1G>A) or *DPYD*13* (c.1679T>G)] will not be able to metabolize fluorouracil at normal rates. Consequently, they are at risk of potentially life-threatening fluorouracil toxicity, such as bone marrow suppression, diarrhea, and neurotoxicity. The prevalence of DPD partial deficiency varies in different populations but is approximately 35%. Complete absence of DPD function, which is often fatal with exposure to 5-FU chemotherapy, occurs in <1% (~0.2%) of the general population.

The FDA-approved drug label for fluorouracil states that no dose of fluorouracil has been proven safe in individuals with absent DPD activity (Table 1). Fluorouracil is contraindicated in individuals who are known to have complete DPD deficiency, or when complete deficiency is suspected because of early-onset or unusually severe fluorouracil toxicity (1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have published dosing recommendations for fluoropyrimidines (fluorouracil and capecitabine) based on *DPYD* genotype (Tables 2 and 3). Both recommendations include dose reductions for intermediate

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metabolizers (with reduced enzyme activity) and avoiding fluorouracil or capecitabine and choosing an alternative agent for poor metabolizers (with absent enzyme activity).

Table 1. The FDA Drug Label for Fluorouracil: Warning DPD Deficiency (2020)

Phenotype	Fluorouracil
DPD deficiency	Increased risk of serious or fatal adverse reactions in individuals with low or absent dihydropyrimidine dehydrogenase (DPD) activity. Withhold or permanently discontinue fluorouracil or its oral pill version capecitabine in individuals with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe in individuals with absent DPD activity.

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This table is adapted from (1).

Table 2. The CPIC Recommended Dosing of Fluoropyrimidines (5-fluorouracil or capecitabine) by DPD Phenotype (2017, Nov 2018 Update)

Phenotype	Implications for phenotypic measures	Activity score	Dosing recommendations	Classification of recommendations[a]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	2	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30–70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	1–1.5	Reduce starting dose by 50%, followed by dose titration based on clinical judgement (and ideally therapeutic drug monitoring) Individuals with homozygous c.[2846A>T];[2846A>T] genotype, a >50% reduction in starting dose may be warranted.	Moderate

Table 2. continued from previous page.

Phenotype	Implications for phenotypic measures	Activity score	Dosing recommendations	Classification of recommendations[a]
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	0.5	Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[c] with early therapeutic drug monitoring.[d]	Strong
		0	Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	

CPIC, Clinical Pharmacogenetics Implementation Consortium
DPD, dihydropyrimidine dehydrogenase.
[a] Rating scheme is described in Supplement (2).
[b] Increase the dose in individuals experiencing no or clinically tolerable toxicity in the first 2 cycles to maintain efficacy; decrease the dose in individuals who do not tolerate the starting dose to minimize toxicities.
[c] If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-flourouracil clearance. [d]Therapeutic drug monitoring should be done at the earliest timepoint possible (for example, minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.
This table is adapted from (2, 3) .
Note: The nomenclature used in this table reflects the standardized nomenclature for pharmacogenetic terms proposed by CPIC in a 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" (4).

Table 3. The DPWG Recommendations for Capecitabine/Fluorouracil by *DPYD* Gene Activity, Systemic Route of Administration (2019)

DPYD gene activity score	Recommendation	Pharmacist text
Activity score 1.5	Start with 50% of the standard dose or avoid fluorouracil and capecitabine. After starting treatment, the dose should be adjusted based on toxicity and effectiveness. Tegafur is not an alternative, as this is also metabolized by DPD.	The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose
Activity score 1.0	Start with 50% of the standard dose or choose an alternative. Adjustment of the initial dose should be guided by toxicity and effectiveness. Tegafur is not an alternative, as this is also metabolized by DPD.	Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.
PHENO[1]	It is not possible to recommend a dose adjustment for these individuals based on the genotype only. Determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose based on phenotype and genotype or avoid fluorouracil and capecitabine. Tegafur is not an alternative, as this is also metabolized by DPD.	The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

Table 3. continued from previous page.

DPYD gene activity score	Recommendation	Pharmacist text
Activity score 0	Avoid fluorouracil and capecitabine Tegafur is not an alternative, as this is also metabolized by DPD. If an alternative is not possible: determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose accordingly. An individual with 0.5% of the normal DPD activity tolerated 0.8% of the standard dose (150 mg capecitabine every 5 days). An individual with undetectable DPD activity tolerated 0.43% of the standard dose (150 mg capecitabine every 5 days with every third dose skipped).	Genetic variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the standard dose is a more than 100-fold overdose.

1 Individual's genotype does not accurately predict activity level, phenotyping required.
Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This table is adapted from (5, 6).
DPWG - Dutch Pharmacogenetics Working Group

Drug Class: Fluoropyrimidines

Fluoropyrimidines are a class of antimetabolite drugs that are widely used in the treatment of cancer. There are 3 types of fluoropyrimidines in clinical use: capecitabine (oral - pill) and 5-fluorouracil (5-FU – IV), which are licensed for use in the US, and tegafur, which is not available in the US. Capecitabine and tegafur are both active precursors of fluorouracil.

Fluoropyrimidines are thought to exert their chemotherapeutic effects in multiple ways, through several active metabolites. The main mechanism of action is thought to be the inhibition of thymidylate synthase, which plays an important part in the folate-homocysteine cycle, and purine and pyrimidine synthesis pathways. Also, active metabolites can be incorporated into RNA and DNA, ultimately leading to cell death (7). Based on their mechanism of action, fluoropyrimidines can cause fetal harm when administered to a pregnant woman (1).

Approximately 10–40% of individuals develop severe and potentially life-threatening toxicity early during treatment with fluoropyrimidines (8). This toxicity typically leads to an interruption or discontinuation of potentially effective anticancer therapy, and may require an emergency room visit or hospitalization in severe instances (9).

The interindividual variation in the occurrence and severity of adverse events in individuals receiving fluoropyrimidines can be partly explained by clinical factors, such as age and gender. However, much of the variability in adverse events remains unexplained (10).

Of the genetic factors thought to contribute to fluoropyrimidine intolerance, the *DPYD* gene has been the most studied. This gene encodes the primary enzyme involved in breaking down fluoropyrimidines to inactive metabolites. Individuals who have a deficiency of the DPD enzyme have a significantly increased risk of suffering from severe fluoropyrimidine toxicity, and the stratification of individuals on the basis of the *DPYD* genotype may help to prevent such adverse events (11, 12, 13, 14, 15, 16).

Drug: Fluorouracil

Fluorouracil is a form of chemotherapy that is given as an IV solution, and is used to manage many cancers, including carcinoma of the colon, rectum, breast, stomach, and pancreas. Fluorouracil may also be used topically as a cream or a solution, for the treatment of multiple actinic or solar keratoses of the face and anterior scalp.

Fluorouracil is structurally similar to pyrimidines, and the enzyme that catalyzes the rate-limiting step in the breakdown of pyrimidines (DPD) also catalyzes the rate-limiting step in 5-FU catabolism. The DPD enzyme catalyzes the conversion of fluorouracil to the non-cytotoxic dihydrofluorouracil (DHFU) (17).

The FDA states that fluorouracil therapy should be discontinued promptly whenever one of the following signs of toxicity appears:

- Cardiotoxicity including angina, myocardial infarction/ischemia, arrhythmia, and heart failure
- Hyperammonemic encephalopathy
- Neurologic toxicity, including acute cerebellar syndrome
- Mucositis, stomatitis or esophagopharyngitis, which may lead to mucosal sloughing or ulceration
- Myelosuppression, which may include neutropenia, thrombocytopenia, and anemia
- Diarrhea (grade 3 or 4), frequent bowel movements, or watery stools
- Palmar-plantar erythrodysesthesia (hand-foot syndrome), grade 2 or 3

The FDA label also indicates that uridine triacetate should be administered within 96 hours following the end of fluorouracil infusion for management of fluorouracil overdose. (1) Uridine triacetate (brand name Vistogard) was approved December 11, 2015 (18). Exogenous uridine competes with 5-FU for incorporation into RNA, thus diluting the toxic effects of high 5-FU levels. Uridine triacetate is 4–6-fold higher in bioavailability than equimolar doses of uridine (19).

Uridine triacetate is meant for overdose treatment of adults or children; however, can be considered in situations of individuals with pharmacogenetic deficiency, which is technically an overdose (20, 21). This compound can also be used in the context of capecitabine overdose (19). The high cost of a single course of uridine triacetate therapy has been cited as a potential barrier to therapy. Nevertheless, 94% of clinical trial participants treated with uridine triacetate survived the overdose event, a notable improvement over the historic mortality rate of 84% (19).

Symptomatic DPD deficiency is a rare autosomal recessive disorder with a wide range of symptoms, ranging from no symptoms or signs, to severe neurological problems. In affected individuals, the absent or greatly decreased DPD activity results in uracil and thymine accumulating in the blood, urine, and cerebrospinal fluid. Neurological symptoms typically manifest in early childhood and include seizures, small head size, and delayed cognitive and motor development (22).

Symptomatic DPD deficiency is typically caused by homozygous inactivation of *DPYD*; whereas individuals who are heterozygotes tend to be asymptomatic. However, all individuals with less than 70% DPD activity are considered at risk for the development of severe drug toxicity when treated with fluoropyrimidines (23). Signs of fluorouracil toxicity include severe diarrhea, severe mucositis, neutropenia, neurotoxicity, and hand-foot syndrome (redness, swelling, and blisters on the palms of the hands an soles of the feet) (1).

Gene: *DPYD*

The *DPYD* gene encodes the enzyme DPD, which catalyzes the first and rate-limiting step in the breakdown of the pyrimidine nucleotides thymine and uracil. The DPD enzyme also catalyzes the rate-limiting step in the breakdown of fluoropyrimidines.

Many *DPYD* variants have been described, although only a few have been demonstrated to influence DPD enzyme activity. When no variant is detected (formerly known as the **1* allele), it is associated with normal enzyme activity. Individuals who have 2 copies of normal activity *DPYD* alleles are known as "normal metabolizers" and have fully functional DPD enzyme activity (Table 4). The *DPYD* alleles c.1601G>A (*4, rs1801158), c.1627G>A (*5, rs1801159), c.2194G>A (*6, rs1801160), and c.85T>C (*9A, rs1801265) are also considered to have normal activity (24). Historically, variant haplotypes in *DPYD* have been identified by their

star (*) allele names. However, the Pharmacogene Variation Database (PharmVar) now identifies these alleles by their dbSNP "rs" allele identifier or cDNA change based on the NM_000110.3 transcript, *DPYD* mRNA variant 1. All 3 of these identifiers are provided in the Nomenclature for Selected *DPYD* alleles table below.

Table 4. Activity Status of Selected *DPYD* Alleles

Allele type	Alleles	
	Strong evidence to support function	Moderate evidence to support function
Normal function	No variant detected (*1), c.1627G>A (*5, rs1801159), c.85T>C (*9A, rs1801265)	c.1601G>A (*4, rs1801158), c.2194G>A (*6, rs1801160), c.1003G>T (*11, rs72549306), c.2657G>A (*9B, rs1801267), 496A>G (rs2297595)
Decreased function	c.2846A>T (rs67376798), 1129-5923C>G and 1236G>A (HapB3)	c.557A>G (rs115232898)
No function	c.1905+1G>A (*2A, rs3918290)	c.1898delC (*3, rs72549303), c.295_298delTCAT (*7, rs72549309), c.703C>T (*8, rs1801266), c.2983G>T (*10, rs1801268), c.1156G>T (*12), c.1679T>G (*13, rs55886062)

This table is adapted from the "*DPYD* Allele Functionality Table", available from CPIC. Additional variant information from the PharmVar database. The cDNA coordinates for variation are given for NM_000110.3, *DPYD* transcript variant 1.
For the nomenclature of human *DPYD* alleles, please see (25).
CPIC, Clinical Pharmacogenetics Implementation Consortium

The non-functional *DPYD* variants that have been associated with absent DPD activity and an increased risk of toxicity with fluoropyrimidines include c.1905+1G>A (*2A, rs3918290) and c.1679T>G (*13, rs55886062) (26). Variants with decreased function include rs67376798 (c.2846A>T) and HapB3, which also are associated with an increased risk of fluoropyrimidine toxicity. The most well studied variant is *DPYD* c.1905+1G>A (*2A, rs3918290), in which a single nucleotide substitution at the invariant splice donor site of intron 14 leads to translation skipping exon 14, resulting in the production of a truncated protein with virtually no enzyme activity.

Individuals who have combinations of one normal function and one decreased function or no function *DPYD* alleles are known as "intermediate metabolizers". Individuals with 2 decreased function alleles are also categorized as intermediate metabolizers. They have partial DPD deficiency and are at increased risk of capecitabine toxicity. And individuals who have a combination of non-functional *DPYD* alleles, or decreased function *DPYD* alleles, or both, are known as "poor metabolizers". They have complete DPD deficiency and are at an even higher risk of capecitabine toxicity.

Activity scores may be used to distinguish between the various *DPYD* alleles and their functionality (Table 5). The use of activity scores may result in differentiated individualized dosing advice for fluoropyrimidines, which is beneficial for reducing toxic side effects while maintaining efficacy (15).

Table 5. Assignment of likely DPD Phenotype based on *DPYD* Genotype (CPIC, 2017)

Likely phenotype	Activity score[a]	Genotype[b]	Examples of genotype[c]
DPYD normal metabolizer	2	An individual with 2 normal function alleles.	c.[=]; [=] c.[85T>C]; [=] c.[1627A>G]; [=]
DPYD intermediate metabolizer (approximately 3–5% of individuals)	1 or 1.5	An individual with one normal function allele plus one no function allele or one decreased function allele, or an individual with 2 decreased function alleles.	c.[1905+1G>A]; [=] c.[1679T>G]; [=] c.[2846A>T]; [=] c.[1129–5923C>G]; [=][d] c.[1129–5923C>G]; [1129–5923C>G][d] c.[2846A>T]; [2846A>T]

Table 5. continued from previous page.

Likely phenotype	Activity score[a]	Genotype[b]	Examples of genotype[c]
DPYD poor metabolizer (approximately 0.2% of individuals)	0 or 0.5	An individual with 2 no function alleles or an individual with one no function plus one decreased function allele.	c.[1905+1G>A]; [1905+1G>A] c.[1679T>G]; [1679T>G] c.[1905+1G>A]; [2846A>T] c.[1905+1G>A]; [1129-5923C>G]

"[ ]" Square brackets are used to indicate an allele, "[=]" Indicates the allele sequence was tested and no changes were found
[a] Calculated as the sum of the 2 lowest individual variant activity scores. See (2) for further information.
[b] Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table)
[c] HGVS nomenclature using the reference sequence NM_000110.3. Note: Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
[d] Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available or other HapB3 proxy SNPs.
This table is adapted from (2).
Note: The nomenclature used in this table reflects the standardized nomenclature for pharmacogenetic terms proposed by CPIC (4).
CPIC, Clinical Pharmacogenetics Implementation Consortium

Overall, the prevalence of individuals who are heterozygous for non-functional *DPYD* alleles (partially DPD deficient) and at risk of severe drug reactions is estimated to be as high as 5–8%, but this varies in different populations (8, 23, 27, 28, 29, 30, 31, 32). In Caucasians, approximately 3–5% of have partial DPD deficiency and 0.2% have complete DPD deficiency (29). Recent studies suggest that ~8% of Caucasians have at least one of the 4 well characterized altered-function alleles (33).

In African-Americans, the prevalence of decreased DPD enzyme activity is 8% (32). It is notable that despite being well studied, *DPYD* c.1905+1G>A (*2A, rs3918290) is incredibly rare in individuals of African ancestry (34). One study reported that the normal function c.85T>C (*9A, rs1801265) allele was present in 49% of African-American samples (35). The rs115232898 (c.557A>G) variant allele with reduced function was detected in 2.6% of African-heritage Brazilians (36).

Studies of Egyptian and Tunisian populations suggest the allelic frequencies for *DPYD* variants in these 2 countries are similar to Caucasian variant allele frequencies (37, 38). The frequency of the poor-metabolizer rs6376798 (c.2846A>T) allele in Mestizo and native Mexican populations is rare, but not significantly different than in MXL (Mexican Ancestry from Los Angeles USA) or CEU (Utah Residents (CEPH) with Northern and Western European Ancestry) populations in the 1000 Genomes Project (39).

Asian populations have slightly different allele frequencies as compared with African and European populations. The frequency of the c.85T>C (*9A, rs1801265) normal function variant was slightly lower in Han Chinese, Korean and Japanese populations, particularly compared with Africans, though the frequency of the c.2657G>A (*9B, rs1801267) normal function variant and c.295_298delTCAT (*7, rs72549309), c.703C>T (*8, rs1801266), and c.2983G>T (*10, rs1801268) no function alleles were similar across these groups (35). The c.1905+1G>A (*2A/*2B, rs3918290) and c.1679T>G (*13, rs55886062) no function alleles were not detected in a study of Hmong and East Asian descent individuals, underscoring the rarity of these alleles (40). An analysis of multiple genotyping studies in South Asian populations found that the rs2297595 (c.496A>G) allele was prevalent in south Asia (41).

Most individuals in the U.S. are not screened for DPD deficiency before starting fluorouracil therapy (42) and the FDA-approved label does not specifically recommend DPD testing (1). In contrast, the European Medicines Agency recommends testing for DPD deficiency before initiating treatment with any fluorouracil related substance via infusion or injection (43).

Gene: *TYMS*

Emerging studies and reports suggest genetic variation at another locus may also affect 5-FU efficacy and toxicity—*TYMS*. This gene encodes thymidylate synthase (TS), which catalyzes the methylation of deoxyuridylate to deoxythymidylate. This reaction is a rate-limiting step in production of an essential DNA synthesis precursor. The TS protein expression correlates positively with sensitivity to 5-FU, and the TS enzyme is one of the targets of 5-FU (44). While this functional link to 5-FU metabolism and tumor response has been demonstrated in multiple studies, the impact of specific genetic variants in *TYMS* is less clear (44, 45, 46, 47). Some *TYMS* alleles have been reported in a handful of studies as being associated with increased toxicity and anti-tumor cell response with fluoropyrimidines.

The rs45445694 variant is the basis of the *TYMS* "2R" allele, which has been associated with clinical response and severe toxicity events, either in homozygosity or heterozygosity (20, 48, 49, 50). This 2R variant occurs in the 5'UTR and is duplication of a 28 base pair (bp) repeat. This same locus can have variable tandem repeats between 0 and 9 copies, and studies suggest that the increased copy number of the repeat is associated with increased *TYMS* expression and TS protein levels (51).

One additional variant in *TYMS* has been found in association with adverse reactions to fluoropyrimidine therapy: a 3'UTR 9bp-indel (rs11280056) (49, 51). There are conflicting reports as to whether this is a 6- or 9-bp indel. One variant (rs2853542) within the *TYMS* enhancer region in the context of the 28bp tandem repeat triplication, called 3RG or 3RC based on the specific nucleotide present, has also been reported in association with neurotoxicity during 5-FU treatment (52). The presence of the C nucleotide at rs2853542 has been associated with decreased expression of *TYMS* mRNA (53).

PharmGKB has described *TYMS* as a 'Very Important Pharmacogene', though the level of evidence for *TYMS* and capecitabine/5-fluorouracil interaction is limited (PharmGKB "level 3") (51). The CPIC also views this interaction as having limited evidence and thus provides no prescribing recommendations for these pharmacogenetic variants (54).

Linking Gene Variation with Treatment Response

Standard doses of fluorouracil increase the risk of severe toxicity in individuals who are carriers of specific *DPYD* variant alleles, and no dose of fluorouracil is considered safe among individuals with absent DPD activity (1, 55). Multiple studies have found that preemptive *DPYD* screening for individuals with cancer can significantly improve individual safety (56, 57, 58, 59, 60, 61). Of note, at least one case report indicated that the cost of administering uridine triacetate and palliative care following an adverse, overdose reaction to 5-FU was roughly $180,000 USD (20).

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for the *DPYD* gene and the fluorouracil drug response. The *DPYD* c.1905+1G>A (*2A, rs3918290) variant is the most commonly tested; however, newly discovered and rare variants may also lead to enzyme inactivation and toxicity to fluoropyrimidine-based chemotherapy (36, 62, 63, 64, 65).

Biochemical genetic tests may also be used, which assess the activity of the DPD enzyme. These tests include biochemical assays such as analyte testing (for example, measuring the amount of thymine and uracil in the urine or blood) or an enzyme assay (for example, directly measuring the activity of DPD using RNA extracted from blood cells and measuring the DPD mRNA copy number) (66, 67, 68).

The GTR provides a list of biochemical tests that assess the levels of thymine and uracil analytes, and the activity of the enzyme DPD.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2020 Statement from the US Food and Drug Administration (FDA)

WARNINGS AND PRECAUTIONS: Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent [Dihydropyrimidine] Dehydrogenase (DPD) Activity

Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD[2] gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

[…]

PATIENT COUNSELING INFORMATION

Advise patients to notify their healthcare provider if they have a known DPD deficiency.

Advise patients if they have complete or near complete absence of DPD activity, they are at an increased risk of severe and life-threatening mucositis, diarrhea, neutropenia and neurotoxicity.

[…]

OVERDOSAGE

Administer uridine triacetate within 96 hours following the end of fluorouracil infusion for management of fluorouracil overdose.

Please review the complete therapeutic recommendations that are located here: (1).

2017 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC), with November 2018 Update

[…]

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

[2] Note: the official gene symbol is *DYPD*, *DPD* is an alternate gene symbol.

Table 2 summarizes the genetics-based dosing recommendations for fluoropyrimidines using the calculated DPYD activity score (DPYD-AS). The strength of the prescribing recommendations is based on the known impact of some variants (c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129–5923C>G) on DPD activity, the demonstrated relationship between DPD activity and 5- fluorouracil clearance, and between 5-fluorouracil exposure and its toxic effects. Patients who are heterozygous for DPYD decreased/no function variants demonstrate partial DPD deficiency and should receive reduced starting doses. Prospective genotyping of c.1905+1G>A followed by a 50% dose reduction in heterozygous carriers resulted in a rate of severe toxicity comparable to noncarriers[see (9)]. This study thus demonstrated that DPYD genetic testing can reduce the occurrence of severe fluoropyrimidine-related toxicity, and that a dose reduction of 50% is suitable for heterozygous carriers of no function variants (DPYD-AS: 1). For decreased function variants, evidence is limited regarding the optimal degree of dose reduction. For c.2846A>T, a small retrospective study observed that the average capecitabine dose in heterozygous carriers was reduced by 25% compared to noncarriers. In a small prospective study, five patients carrying c.1236G>A (proxy for c.1129–5923C>G) were safely treated with a 25% reduced capecitabine starting dose. This suggests that heterozygous carriers of decreased function variants (DPYD-AS: 1.5) may tolerate higher doses com- pared to carriers of no function variants (DPYD-AS: 1). In patients with DPYD-AS of 1.5, the individual circumstances of a given patient should therefore be considered to determine if a more cautious approach (50% starting dose followed by dose titration), or an approach maximizing potential effectiveness with a potentially higher toxicity risk (25% dose reduction) is preferable. Of note, both studies indicating the suitability of a 25% dose reduction in decreased function variant carriers included only patients receiving capecitabine and no data are currently available for infusional 5-fluorouracil.

Given that some patients carrying decreased or no function variants tolerate normal doses of 5-fluorouracil, to maintain effectiveness, doses should be increased in subsequent cycles in patients experiencing no or clinically tolerable toxicity in the first two chemotherapy cycles or with subtherapeutic plasma concentrations. Similarly, doses should be decreased in patients who do not tolerate the starting dose.

In DPYD poor metabolizers (DPYD-AS: 0.5 or 0), it is strongly recommended to avoid use of 5-fluorouracil-containing regimens. However, if no fluoropyrimidine-free regimens are considered a suitable therapeutic option, 5-fluorouracil administration at a strongly reduced dose combined with early therapeutic drug monitoring may be considered for patients with DPYD-AS of 0.5. It should be noted, however, that no reports of the successful administration of low-dose 5-fluorouracil in DPYD poor metabolizers are available to date. Assuming additive effects of decreased and no function alleles (DPYD-AS: 0.5), it is estimated that a dose reduction of at least 75% would be required (i.e., starting dose <25% of normal dose). Furthermore, in such cases a phenotyping test is advisable to estimate DPD activity and a starting dose.

The US Food and Drug Administration (FDA) and the Health Canada Santé Canada (HCSC) have added statements to the drug labels for 5-fluorouracil and capecitabine that warn against use in patients with DPD deficiency, and prescribing recommendations for 5-fluorouracil, capecitabine, and tegafur are also available from the Dutch Pharmacogenetics Working Group.

November 2018 Update:

The current DPYD guideline recommends to reduce the dose of fluoropyrimidines by 25-50% (from the full standard dose) in DPYD Intermediate Metabolizers with an activity score of 1.5. At the time of the guideline publication, this dose range was recommended due to limited evidence for genotype-guided dosing of decreased function alleles/variants. However, a recent prospective study (PMID: 30348537) provides evidence to support a recommendation for a 50% dose reduction in heterozygous carriers of the decreased function variants c.2846A>T (rs67376798) or c.1129–5923C>G (rs75017182; HapB3 or its tagging SNP c.1236G>A; rs56038477). These data suggest that all Intermediate Metabolizers with an activity score of 1.5 should receive a 50% dose reduction.

Therefore CPIC revises its recommendation such that all DPYD Intermediate Metabolizers should receive a 50% dose reduction from the full standard starting dose, whether the activity score is 1 or 1.5 followed by dose titration, based on clinical judgement and ideally therapeutic drug monitoring.

In addition, recent case reports from patients who are homozygous for c.2846A>T (activity score of 1) indicate that a dose reduction of more than 50% may be required in some carriers of this genotype. Therefore, in patients with an activity score of 1 due to a homozygous c.[2846A>T];[2846A>T] genotype, clinicians should be aware that a >50% reduction in starting dose might be warranted.

Please review the complete therapeutic recommendations that are located here: (2, 3)

2019 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

DPD Gene Activity Score 0

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the standard dose is a more than 100-fold overdose.

- Avoid fluorouracil and capecitabine

Tegafur is not an alternative, as this is also metabolized by DPD.

- If it is not possible to avoid fluorouracil and capecitabine: determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose accordingly.

A patient with 0.5% of the normal DPD activity tolerated 0.8% of the standard dose (150 mg capecitabine every 5 days). A patient with undetectable DPD activity tolerated 0.43% of the standard dose (150 mg capecitabine every 5 days with every third dose skipped)

DPD [PHENO] [phenotyping indicates reduced function]

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

It is not possible to recommend a dose adjustment for this patient based on the genotype only.

- determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose based on phenotype and genotype, or avoid fluorouracil and capecitabine.

Tegafur is not an alternative, as this is also metabolized by DPD.

DPD Gene Activity Score 1

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

- Start with 50% of the standard dose or avoid fluorouracil and capecitabine.

Adjustment of the subsequent dose should be guided by toxicity and effectiveness. However, in one study involving 17 patients with gene activity 1, the average dose after titration was 57% of the standard dose.

Tegafur is not an alternative, as this is also metabolized by DPD.

DPD Gene Activity Score 1.5

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

- Start with 50% of the standard dose or avoid fluorouracil and capecitabine.

After starting treatment, the dose should be adjusted based on toxicity and effectiveness. In a study involving 17 patients with genotype *1/2846T*, the average dose after titration was 64% of the standard dose. For 51 patients with genotype *1/1236A*, the average dose after titration was 74% of the standard dose. Tegafur is not an alternative, as this is also metabolized by DPD.

DPD Gene Activity Score 0 (Cutaneous fluorouracil)

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

- avoid fluorouracil

NOTE: If a patient has two different genetic variations that lead to a non-functional DPD enzyme (e.g. *2A and *13), this recommendation only applies if the variations are on a different allele. If both variations are on the same allele, this patient actually has a gene activity score 1, for which no increased risk of severe, potentially fatal toxicity has been found with cutaneous use. These two situations can only be distinguished by determining the enzyme activity (phenotyping). This recommendation only applies if the patient has virtually no enzyme activity.

Background Information - Mechanism

Fluorouracil is mainly (> 80%) converted by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites. Lower metabolic activity of DPD leads to increased intracellular concentrations of fluorodeoxyuridine monophosphate, the active metabolite of fluorouracil and its prodrug capecitabine. This leads to an increased risk of adverse events such as neutropenia, thrombopenia and hand-foot syndrome.

For more information about the phenotype gene activity score: see the general background information about DPD on the KNMP Knowledge Bank or on www.knmp.nl (search for DPD).

Please review the complete therapeutic recommendations that are located here: (5) .

Nomenclature for Selected Alleles

***DPYD* Alleles**

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
rs3918290	*DPYD*2A*, c.1905+1G>A	NM_000110.4:c.1905+1G>A	Not applicable—deletion of exon 14 leads to the production of a truncated protein	rs3918290
	IVS14+1G>A			
rs55886062	*DPYD*13*, c.1679T>G, rs55886062.1, p.Ile560Ser	NM_000110.4:c.1679T>G	NP_000101.2:p.Ile560Ser	rs55886062
rs67376798	c.2846A>T p.Asp949Val	NM_000110.4:c.2846A>T	NP_000101.2:p.Asp949Val	rs67376798
rs75017182	c.1129–5923C>G	NM_000110.4:c.1129-5923C>G		rs75017182
rs1801159	*DPYD*5*, c.1627G>A	NM_000110.4:c.1627A>G	NP_000101.2:p.Ile543Val	rs1801159
rs1801265	*DPYD*9A*, c.85T>C	NM_000110.4:c.85T>C	NP_000101.2:p.Cys29Arg	rs1801265

DPYD Alleles continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
rs1801158	*DPYD*4*, c.1601G>A	NM_000110.4:c.1601G>A	NP_000101.2:p.Ser534Asn	rs1801158
rs1801160	*DPYD*6*, c.2194G>A	NM_000110.4:c.2194G>A	NP_000101.2:p.Val732Ile	rs1801160
rs72549306	*DPYD*11*, c.1003G>T, rs72549306.1	NM_000110.4:c.1003G>T	NP_000101.2:p.Val335Leu	rs72549306
rs1801267	*DPYD*9B*, c.2657G>A	NM_000110.4:c.2657G>A	NP_000101.2:p.Arg886His	rs1801267
rs72549303	*DPYD*3*, c.1898delC	NM_000110.4:c.1898del	NP_000101.2:p.Pro633fs	rs72549303
rs72549309	*DPYD*7*, c.295_298delTCAT	NM_000110.4:c.295_298TCAT[1]	NP_000101.2:p.Phe100fs	rs72549309
rs1801266	*DPYD*8*, c.703C>T	NM_000110.4:c.703C>T	NP_000101.2:p.Arg235Trp	rs1801266
rs1801268	*DPYD*10*, c.2983G>T	NM_000110.4:c.2983G>T	NP_000101.2:p.Val995Phe	rs1801268
rs78060119	*DPYD*12*, c.1156G>T	NM_000110.4:c.1156G>T	NP_000101.2:p.Glu386Ter	rs78060119
rs115232898	557A>G (Y186C)	NM_000110.4:c.557A>G	NP_000101.2:p.Tyr186Cys	rs115232898
rs2297595	496A>G (M166V)	NM_000110.4:c.496A>G	NP_000101.2:p.Met166Val	rs2297595
rs75017182 rs56038477	HapB3 1129-5923C>G 1236G>A	NM_000110.4:c.1129-5923C>G NM_000110.4:c.1236G>A	Altered mRNA splicing due to cryptic splice donor site leads to retention of intronic sequence, introduces premature termination codon in resulting protein.	rs75017182 rs56038477
			NP_000101.2:p.Glu412=	

TYMS Alleles

Common allele name	Alternative names	HGVS reference sequence	dbSNP reference identifier for allele location
rs45445694	2R, 3R *TYMS* 5'UTR	GRCh37.p13 chr 18, NC_000018.9:g.657657_657712del, NC_000018.9:g.657657_657684GGCCTGCCTCCGTCCCGCCGCGCCACTT[1]-[9] #	rs45445694
rs11280056	*TYMS* 3'UTR	GRCh37.p13 chr 18, NC_000018.9:g.673447_673452del, NC_000018.9:g.673447_673452dup# NM_017512.7:c.*856_*861del	rs11280056
rs2853542	*TYMS* 3RG, 3RC	GRCh37.p13 chr 18, NC_000018.9:g.657685G>C# NM_001071.4:c.-58=	rs2853542

This is a non-coding variant in the *TYMS* untranslated region. Coordinates given are chromosomal.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (69).
Allele information for *DPYD* can also be found at the Pharmacogene Variation Consortium (PharmVar).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

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Version History

To view the 2016 version of this summary (created 3 November 2016), please click here.

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