

Clinical Commissioning Urgent Policy Statement

Pharmacogenomic testing for *DYPD* polymorphisms with fluoropyrimidine therapies [URN 1869] (200603P)

Commissioning position

Summary

Pharmacogenomic testing for *DYPD* polymorphisms which cause dihydropyrimidine dehydrogenase (DPD) deficiency is recommended to be available through routine commissioning as a pre-treatment screening test prior to the administration of fluoropyrimidine-based therapies through routine commissioning within the criteria set out in this document.

Information about pharmacogenomic testing for *DYPD* polymorphisms with fluoropyrimidine therapies

The intervention

Fluoropyrimidines (5-fluorouracil, capecitabine and tegafur) are antimetabolite chemotherapy drugs which are used in the treatment of various cancers. Approximately 38,000 patients are initiated on fluoropyrimidine-based therapy each year in England (Public Health England, 2020).

Fluoropyrimidines have a narrow therapeutic window between the minimum effective and maximum tolerated doses. The enzyme dihydroprimidine dehydrogenase (DPD) plays a key role in the metabolism of fluoropyrimidine drugs, inactivating approximately 80% of 5-fluorouracil (Lunenburg 2020). However, some patients have a reduced level of the DPD enzyme. Variants in the *DYPD* gene which encodes the DPD enzyme have been associated with reduced enzyme activity, leading to an increased risk of severe and even fatal toxicity in patients receiving fluoropyrimidine treatment (Amstutz 2018).

Pre-emptive pharmacogenomic testing of specific *DYPD* variants would alert clinicians to patients with a genetic susceptibility to severe fluoropyrimidine toxicity, allowing dose adjustments or selection of an alternative treatment regimen as deemed clinically appropriate.

The following fluoropyrimidines have not been included within the scope of this policy proposition:

- Topical fluorouracil cream – pre-treatment screening is not required as systemic absorption is very low and the safety of topical fluorouracil is not expected to change in patients with partial or complete DPD deficiency (European Medicines Agency, 2020).
- Flucytosine – routine pre-treatment screening is not recommended as treatment for severe fungal infections should not be delayed (European Medicines Agency, 2020).

Committee discussion

The Clinical Panel considered the Preliminary Policy Proposal which was submitted as an urgent policy request. It was agreed that this would proceed as a 3 paper evidence review. It was recommended this proceed as an urgent interim policy statement.

The condition

Fluoropyrimidines are used as part of the treatment of various cancers including:

- colorectal cancer;
- oesophago-gastric cancer;
- breast cancer;

OFFICIAL

- cancers of the head and neck

Approximately 10-40% of fluoropyrimidine-treated patients develop severe or life-threatening toxicity, symptoms of which include neutropenia, nausea, vomiting, diarrhoea, stomatitis, mucositis and hand-foot syndrome (Amstutz 2018). Toxicity is fatal in 1% of patients (Lunenburg 2020).

Current treatments

Fluorouracil, capecitabine and tegafur are contraindicated in patients with known complete absence of DPD activity due to the risk of severe, life-threatening or fatal adverse reactions. Caution is recommended in patients with partial DPD deficiency, with consideration of dose reduction and increased monitoring. Four *DYPD* variants associated with DPD deficiency are specified within the product licensing (European Medicines Agency 2020). In March 2020, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended that patients should be tested for DPD deficiency prior to starting fluoropyrimidine chemotherapy (European Medicines Agency 2020).

For patients who experience severe toxicity, the current standard treatment is symptomatic relief and supportive care. The drug uridine triacetate is approved for severe or life-threatening adverse events occurring within 96 hours of fluoropyrimidine treatment under specific criteria. Pre-emptive testing of *DYPD* variants is likely to reduce the requirement for uridine triacetate administration and reduce mortality and morbidity associated with fluoropyrimidine treatment.

Comparators

Not applicable.

Clinical trial evidence

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) both conducted systematic reviews of the literature to form their guidelines in 2017 and 2019 respectively (Amstutz 2018; Lunenburg 2020). These two groups provide recommendations on the *DYPD* variants for which there is robust evidence of association with fluoropyrimidine-toxicity (See Appendix 1: Evidence Summary).

Three key clinical studies provide evidence of the clinical utility of *DYPD* testing to reduce the incidence of severe fluoropyrimidine-associated toxicity. These are summarised below, with further details available in the evidence summary (Appendix 1).

Meulendijks et al (2015) conducted a systematic review and meta-analysis of cohort studies investigating *DYPD* variants as predictors of severe (grade ≥ 3) fluoropyrimidine-associated toxicity, pooling 7365 patients from 8 studies. The study found a significant association for 2 variants with severe fluoropyrimidine-associated toxicity; c.1679T>G (adjusted RR 4.40; p<0.0001) and c.1236G>A/HapB3 (adjusted RR 1.59; p<0.0001). The variant c.1601G>A was not significantly associated with fluoropyrimidine toxicity (p=0.15).

Deenen et al (2016) conducted a prospective, cohort study assessing the safety, feasibility and cost of prospective genotyping for c.1905+1G>A prior to fluoropyrimidine therapy. A total of 2038 patients were genotyped, of whom 22 were heterozygous variant carriers. Grade ≥ 3 toxicity occurred in 5/18 (28%) of the variant carriers who received fluoropyrimidine treatment.

This data was compared against historical controls (n=3974) within which 48 variant carriers had received fluoropyrimidine treatment at full standard dose. The incidence of grade ≥ 3 toxicity was reduced from 73% in variant carriers receiving standard dose to 28% by genotype-guided dosing (p<0.001). There was also a reduction in death from 10% (5/48) in historical controls compared with none (0%; 0/22) in the genotype-guided dosing arm. The toxicity profile with genotype-guided dosing strategy was comparable to the historical wild-type controls.

OFFICIAL

Henricks et al (2018) reported findings from a prospective, cohort safety analysis on the effects of pre-emptive *DYPD* genotype testing and dose adjustment in patients on fluoropyrimidine therapy. Patients had a genotype test for four *DYPD* variants prior to starting fluoropyrimidine therapy. 1103 patients were evaluated, of whom 85 (8%) were heterozygous *DYPD* variant allele carriers.

Overall incidence of severe fluoropyrimidine-related toxicity was significantly higher in *DYPD* variant allele carriers 33/85 (39%) compared to wild-type patients 231/1018 (23%) ($p=0.0013$). The relative risk of severe toxicity in the *DYPD* variant cohort was compared with a historical cohort of variant carriers who received full standard dose therapy. Genotype guided dosing reduced the relative risk of severe toxicity in c.1905+1G>A carriers from 2.87 with full dose to 1.31 with genotype-guided dosing.

Implementation

Criteria

All patients, prior to commencing treatment with a fluoropyrimidine based therapy (5-fluorouracil, capecitabine or tegafur) should be screened for the following four *DYPD* gene variants which have been associated with fluoropyrimidine-associated toxicity.

- c. 1905+ 1G>A (rs3918290) *DYPD**2A
- c. 2846A>T (rs67376798)
- c.1679T>G (rs55886062) *DYPD**13
- c.1236G>A/HapB3DPYD (rs56038477)

Patients only require this test to be carried out once, at the start of their first fluoropyrimidine treatment, as the results remain applicable to subsequent fluoropyrimidine cycles and future treatment regimens containing a fluoropyrimidine.

A combined test for these 4 variants is estimated to predict 20-30% of early-onset life-threatening 5-fluorouracil toxicities (Amstutz 2018, Froehlich 2015). It is also estimated to predict severe (grade ≥ 3) fluoropyrimidine toxicities (Meulendijks 2015; Deenen 2016; Henricks 2018).

The absence of these four genetic variants does not eliminate the risk of toxicity. Response to fluoropyrimidine therapy and presence of DPD deficiency is also influenced by other genetic, physiological and environmental factors. Individual patient factors and drug-drug interactions must also be taken into account when selecting appropriate regimens and dosing, using a shared-decision making approach.

The majority of evidence linked to these four *DYPD* variants is in white Caucasian populations. The frequency of various *DYPD* variants and associated phenotypes varies significantly between different ethnic groups and this should be considered in clinical decision making (Amstutz 2018).

Genomic test implementation

This test will be made routinely available via the seven national NHS Genomic Laboratory Hubs (GLHs) in England. Information on the test and appropriate genetic testing technology will be updated within the National Genomic Test Directory. Within the clinical pathway, the test should be ordered for eligible patients at the point of consent for fluoropyrimidine chemotherapy or earlier if appropriate.

OFFICIAL

Clinical guidance to support test interpretation & dose adjustments

Guidance for clinicians on test interpretation and dose adjustments for fluoropyrimidine therapy following detection of a *DPYD* variant will be published by the UK Chemotherapy Board to support implementation of this policy <https://www.ukchemotherapyboard.org/publications>

Effective from

The policy statement is effective from August 2020.

Recommendations for data collection

NHS GLHs will collect data on the number of tests, requesting specialties, turnaround times and test outcome as part of existing contractual datasets.

It is further recommended that clinical data on prescribing decisions (e.g. dose adjustments), and patient toxicity are monitored, to inform requirement of further amendments to the testing strategy. An implementation strategy for clinical data collection, using existing datasets where possible, is under review by the Chemotherapy and Genomics CRGs.

Mechanism for funding

Testing will be funded by Regional Commissioning Teams through established funding processes.

Policy review date

This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net. This policy will additionally be kept under review as part of the annual review process for the National Genomic Test Directory.

Links to other policies

Not applicable.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Appendix 1: Evidence summary

Clinical evidence

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) both conducted systematic reviews of the literature to form their guidelines in 2017 and 2019 respectively (Amstutz 2018; Lunenburg 2020). These two groups provide recommendations on the DPYD variants for which there is robust evidence of association with fluoropyrimidine-toxicity (Table 1) and suggest dosing adjustments in patients who carry these variants.

Three key clinical studies provide evidence of the clinical utility of *DPYD* testing to reduce the incidence of severe fluoropyrimidine-associated toxicity.

Meulendijks et al (2015) conducted a systematic review and meta-analysis of cohort studies investigating *DPYD* variants as predictors of severe (grade ≥ 3) fluoropyrimidine-associated toxicity. The meta-analysis focused on 3 variants (c.1679T>G, c.1236G>A/HapB3, and c.1601G>A) and pooled 7365 patients from 8 studies.

The study found a significant association between c.1679T>G (adjusted RR 4.40; 95% CI 2.08 to 9.30; $p<0.0001$) and c.1236G>A/HapB3 (adjusted RR 1.59; 95% CI 1.29 to 1.97; $p<0.0001$) and severe fluoropyrimidine-associated toxicity. In particular there was an increased risk of severe gastrointestinal and haematological toxicity in patients with these variants. The variant c.1601G>A was not significantly associated with fluoropyrimidine toxicity ($p=0.15$).

Deenen et al (2016) conducted a prospective, multi-centre, cohort study in the Netherlands assessing the safety, feasibility and cost of prospective genotyping for c.1905+1G>A prior to fluoropyrimidine therapy. All tumour types and fluoropyrimidine-based therapy regimens were eligible for the study. The primary endpoint was severe (grade ≥ 3) fluoropyrimidine-associated toxicity. An initial $\geq 50\%$ dose reduction was recommended for heterozygous variant allele carriers, with further dose escalation permitted if the first two cycles were well tolerated at the clinicians discretion. For homozygous variant allele carriers a minimal dose reduction of 85% was advised.

A total of 2038 patients were genotyped, of whom 22 were heterozygous variant carriers. No homozygous variant carriers were identified. The most prevalent tumour type was colorectal cancer (53%) and 90% of patients were treated with a capecitabine-based regimen. Grade ≥ 3 toxicity occurred in 5/18 (28%) of the variant carriers who received fluoropyrimidine treatment.

This data was compared against historical controls (n=3974) within which 48 variant carriers had received fluoropyrimidine treatment at full standard dose. The incidence of grade ≥ 3 toxicity was reduced from 73% (95% CI 58% to 85%) in variant carriers receiving standard dose to 28% (95%CI 10% to 53%) by genotype-guided dosing ($p<0.001$). There was also a reduction in death from 10% (5/48) in historical controls compared with none (0%; 0/22) in the genotype-guided dosing arm. The toxicity profile with genotype-guided dosing strategy was comparable to the historical wild-type controls (grade ≥ 3 toxicity 28% vs 23%; $p=0.64$). Pharmacokinetic analysis in 16/22 variant carriers demonstrated a two-fold increase in exposure to 5-FU compared to controls, indicating a 50% dose reduction is appropriate. The cost-analysis predicted a cost saving of €45 per patient when comparing the average treatment costs of the genotype screening strategy to non-screening (€2,772 vs €2,817).

OFFICIAL

In a follow up matched-pair study by Henricks et al (2019), c.1905+1G>A variant carriers (n=37) who received genotype-guided dosing were matched with wild-type patients to assess treatment outcome. There was no significant difference between the genotype-guided dosing group and wild-type controls in overall survival (median 27 vs 24 months; p =0.47) or progression-free survival (median 14 months vs 10 months; p=0.54) respectively. These results suggest that genotype-guided dose reductions for c.1905+1G>A do not negatively impact on treatment outcome.

Henricks et al (2018) reported findings from a prospective, multicentre, cohort safety analysis in the Netherlands on the effects of pre-emptive *DYPD* genotype testing and dose adjustment in patients on fluoropyrimidine therapy. All tumour types and fluoropyrimidine-based therapy regimens were eligible for the study. Patients who had received prior treatment with fluoropyrimidines were excluded.

Patients had a genotype test for the four *DYPD* variants in table 1 prior to starting fluoropyrimidine therapy. Heterozygous *DYPD* variant carriers received initial dose reductions in line with CPIC guidance. Homozygous and compound heterozygous variant allele carriers (n=4) were excluded from the study and treated via alternative personalised dosing regimens.

The primary endpoint was severe (grade ≥ 3) fluoropyrimidine-associated toxicity. 1103 patients were evaluated, of whom 85 (8%) were heterozygous *DYPD* variant allele carriers and 1018 (92%) were *DYPD* wild-type patients. The most common tumour type was colorectal cancer (64%) and 83% (915/1103) of patients were treated with a capecitabine-based regimen. Median follow up was for 71 days (IQR 36-161 days).

Overall 33/85 (39%) of *DYPD* variant allele carriers had severe fluoropyrimidine-related toxicity, which was significantly higher when compared to 231/1018 (23%) of wild type patients (p=0.0013). Incidence of grade 4 or higher toxicity was similar in both groups (p=0.49). Hospital admission as a result of fluoropyrimidine toxicity was more frequent in the *DYPD* variant group (16/85; 19%) compared to the wild-type group (140/1018; 14%), although not statistically significant (p=0.26). Fluoropyrimidine discontinuation rates due to adverse events were similar in both arms.

The relative risk of severe toxicity in the *DYPD* variant cohort was compared with a historical cohort of variant carriers who received full standard dose therapy. Genotype guided dosing reduced the relative risk of severe toxicity in c.1905+1G>A carriers from 2.87 (95% CI 2.14 to 3.86) with full dose to 1.31 (95% CI 0.63 to 2.73) with genotype-guided dosing. A reduction in toxicity risk comparable to *DYPD* wild-type patients was not identified for the other variants. In c.1236G>A carriers there was no reduction in toxicity risk with dose reductions. In c.2846A>T carriers, the toxicity risk was reduced by genotype-guided dosing but still remained higher than the wild-type group. The authors noted that the 25% dose reduction recommended for these 2 variants may be insufficient for some patients.

Limited pharmacokinetic data from a small subgroup of patients (26/85) with *DYPD* variants suggest that genotype-guided dose reduction did not result in undertreatment. However, the study was underpowered to reach a robust conclusion.

Evidence for Variants

CPIC and DPWG conducted a systematic review of *DYPD* variants, and both groups concluded within their guidelines that the four variants in table 1 currently have sufficiently robust evidence of association with fluoropyrimidine toxicity to warrant pharmacogenomic testing for 5-fluorouracil and capecitabine (Amstutz 2018; Lunenburg 2020). These four variants are also specified in the product licenses for capecitabine and 5-fluorouracil as having a known association with toxicity due to low or partial DPD deficiency (European Medicines Agency 2020).

OFFICIAL

Evidence to support routine testing for the *DYPD* c.1601G>A (rs1801158) allele was considered insufficient at present within the systematic reviews conducted by both CPIC and DPWG (Amstutz 2018; Lunenburg 2020), and in the study by Meulendijks et al (2015).⁵

Table 1: DYPD variants with robust evidence of association with fluoropyrimidine toxicity (Amstutz 2018; Lunenburg 2020)

Gene	Nucleotide Change	rsID	Allele associated DPD enzyme activity	CPIC Allele score	CPIC evidence level	DPWG evidence level
<i>DYPD</i>	c.1905+1G>A (<i>DYPD</i> *2A)	rs3918290	No function	0	Strong	Moderate
<i>DYPD</i>	c.1679T>G (<i>DYPD</i> *13)	rs55886062	No function	0	Strong	Moderate
<i>DYPD</i>	c.2846A>T	rs67376798	Reduced function	0.5	Strong	Moderate
<i>DYPD</i>	c.1129-5923C>G & c.1236G>A* (<i>HapB3 haplotype</i>)	rs75017182, rs56038477	Reduced function	0.5	Strong	Moderate

*These two variants are within the HapB3 haplotype; c.1129-5923C>G is the likely causative variant and c.1236G>A sits in linkage disequilibrium with this variant and can therefore be used as a proxy. Both these variants should be considered as one haplotype variant for interpretation.³

A combined test for these 4 variants is estimated to predict 20-30% of early-onset life-threatening 5-fluorouracil toxicities (Amstutz 2018, Froehlich 2015). DPWG calculated the number needed to genotype to prevent an adverse event as 53.9, and designated *DYPD* testing for fluoropyrimidine therapy (5-fluorouracil and capecitabine) as 'essential' for clinical implication (Lunenburg 2020). Existing evidence for variants relates primarily to 5-fluorouracil and capecitabine. There is limited evidence for tegafur, however these four variants are recommended by the EMA for genotypic testing within the licensing for tegafur.

Of note, the absence of tested variants does not eliminate the risk of toxicity, as other genetic, physiological and environmental factors also contribute to DPD deficiency.

Phenotypic DPD testing

There are several phenotypic tests which also assess DPD activity. Of these, the measurement of endogenous dihydrouracil/uracil ratio (UH2/U) in plasma is considered the most feasible for clinical implementation (Meulendijks 2016). However, studies to date have shown variation in the mean and range of endogenous UH2/U ratios, and in correlation between UH2/U ratio and 5-fluorouracil concentrations and resultant toxicity (van Staveren 2013; Meulendijks 2016; Amstutz 2018; Wigle 2019). Measurement of endogenous uracil (U) in plasma is another phenotypic testing option, however there are uncertainties in the uracil thresholds defining complete and partial DPD deficiency and the translation of these into clinical dose adjustments of fluoropyrimidines (Meulendijks 2017). Combined genotypic and phenotypic testing may improve sensitivity of DPD deficiency diagnostic testing, however further evidence of clinical validity and utility of phenotypic testing is required before this is implemented. (van Staveren 2013; Meulendijks 2016; Amstutz 2018; Coenen 2018; Wigle 2019)

Prevalence of variants by ethnicity

The majority of evidence linked to these four *DPYD* variants is in white Caucasian populations. The prevalence of DPD deficiency and frequency of various *DPYD* variants and associated phenotypes varies significantly between different ethnic groups (Amstutz 2018; Mattison 2006). Several studies have investigated the prevalence of *DPYD* variants in non-Caucasian groups (Offer 2013; Elraiayah 2017; Nahid 2018; Salehifar 2018), however further evidence is still required to establish the frequency and clinical application (Amstutz 2018).

Table 2: Prevalence of DPYD Variants by Ethnicity

DPYD Variant	Total Minor Allele Frequency (Ensembl Genome Browser 2020)	Minor Allele Frequency by Ethnicity (Amstutz 2019)					
		African American/Afro-Caribbean	Central/South Asian	East Asian	European	Latino	Sub-Saharan African
c.1905+1G>A (rs3918290)	0.3 – 0.6%	0.3%	0.5%	0%	0.8%	0.08%	0%
c.1679T>G (rs55886062)	0.01 – 0.03%	0%	0%	0%	0.06%	0%	0%
c.2846A>T (rs67376798)	0.2 – 0.3%	0.3%	0.06%	0%	0.4%	0.2%	0%
c.1129-5923C>G (rs75017182) c.1236G>A (rs56038477)	1%	0.3%	2%	0%	2%	0.6%	0%

Evidence in paediatrics

5-fluorouracil, capecitabine and tegafur are not currently licensed for use in paediatric patients. There is limited data on *DPYD* genetic variation and 5-fluorouracil toxicity in paediatric populations (Lunenburg 2020).

References

- Amstutz, U. et al. (2018) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* 103(2), 210-216.
- Amstutz, U. et al. (2019) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. DPYD Allele Functionality Table. [Accessed 12 December 2020]. Available from: <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>.
- Coenen, M.J.H. et al. (2018) Evolution of Dihydropyrimidine Dehydrogenase Diagnostic Testing in a Single Center during an 8-Year Period of Time. *Curr Ther Res Clin Exp.* 90, 1-7.
- Deenen, M.J. et al. (2016) Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. *J Clin Oncol.* 34(3), 227-34.
- Elraiayah, T. et al. (2017) Novel deleterious Dihydropyrimidine Dehydrogenase Variants May Contribute to 5-Fluorouracil Sensitivity in an East African Population. *Clin Pharmacol Ther.* 101(3), 382-390.
- Ensembl Genome Browser. Data from 1000 Genomes and gnomAD Genome Databases. [Accessed 12 December 2020]. Available from: <https://www.ensembl.org/index.html>
- European Medicines Agency. (2020) Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. [Viewed 20 May 2020]. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal>
- Froehlich, T.K. et al. (2015) Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. *Int J Cancer.* 136(3), 730-9.
- Henricks, L.M. et al. (2018) DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol.* 19(11), 1459-1467.
- Henricks, L.M. et al. (2019) Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *Int J Cancer.* 144 (9), 2347-2354.
- Lunenburg CATC et al. (2020) Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. *Eur J Hum Genet.* 28, 508-517.

OFFICIAL

Mattison, L.K et al. (2006) Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African-Americans compared with Caucasians. *Clin Cancer Res.* 12(18), 5491-5.

Meulendijks, D. et al. (2015) Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *Lancet Oncol.* 16(16), 1639-50.

Meulendijks, D. et al. (2016) Improving safety of fluoropyrimidine chemotherapy by individualizing treatment based on dihydropyrimidine dehydrogenase activity - Ready for clinical practice? *Cancer Treat Rev.* 50, 23-34.

Meulendijks, D. et al. (2017) Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. *Br J Cancer.* 116(11), 1415-1424.

Nahid, N.A. et al. (2018) DPYD*2A and MTHFR C677T predict toxicity and efficacy, respectively, in patients on chemotherapy with 5-fluorouracil for colorectal cancer. *Cancer Chemother Pharmacol.* 81(1), 119-129.

Offer, S.M. et al. (2013) A DPYD variant (Y186C) in individuals of african ancestry is associated with reduced DPD enzyme activity. *Clin Pharmacol Ther.* 94(1), 158-66.

Public Health England Systemic Anticancer Therapy Dataset. Enquiry: SACT Data Counts. Data for 2018/19 for England. [Extracted on 29 November 2019].

Salehifar, E. et al. (2018) Dihydropyrimidine Dehydrogenase Gene Variation and its Association with 5-Fluorouracil Toxicity in Colorectal Patients. *Asian Pac J Cancer Biol.* 3(3), 65-69.

van Staveren, M.C. et al. (2013) Evaluation of predictive tests for screening for dihydropyrimidine dehydrogenase deficiency. *Pharmacogenomics J.* 13(5), 389-95.

Wigle, T.J. et al. (2019) DPYD and Fluorouracil-Based Chemotherapy: Mini Review and Case Report. *Pharmaceutics.* 11(5), 199.