Personalised Medicine Approach for Fluoropyrimidine-based Therapies

This document has been endorsed by the UK SACT board member organisations. It is recommended that all Hospital trusts and organisations should adopt this guidance for local use.

The document was originally based on local guidelines from Guy's & St Thomas' NHS Foundation Trust and recommendations from the European Medicines Agency published 30th April 2020 [1,2]. This updated version takes into account new evidence around specific genetic variants published by the Clinical Pharmacogenomics Implementation Consortium in January 2024 and work undertaken as part of a NHS England funded transformation programme into the use of *DPYD* testing [3].

Objective:

To provide clinical staff with guidance as to which patients should receive a *DPYD* test and then subsequently to provide advice to clinical staff on the outcome of that test.

Scope:

This guidance covers all necessary tumour groups and is relevant to all clinical staff involved with the management of patients within these tumour groups.

Responsibilities:

Clinical staff member	Responsibility
SACT lead and Lead nurse or Matron for SACT.	To ensure that this procedure has been highlighted and made available to all members of staff.
Consultant	Ensuring their team are aware that each patient due to receive a fluoropyrimidine has a *DPYD* test prior to starting treatment. This includes explaining the test to the patient, ordering the test and then following up with the test outcome.
Prescriber including Specialist Registrar or Independent non-medical Prescriber	Explaining the test to the patient, ordering the test and then following up with the test outcome.

Pharmacist	During clinical verification of a prescription containing a fluoropyrimidine, ensuring a DPD test is taken prior to cycle 1. If this has not been done, contacting the consultant for advice on how to proceed.
Chemotherapy nurse	Prior to administration of a fluoropyrimidine for the first cycle, ensuring a DPD test has been done and liaising with pharmacy and the medical team if a DPD test has not been taken or the result is unavailable.

A Best Practice Pathway for implementation of *DPYD* testing within fluoropyrimidine pathways is included in Appendix 1

Abbreviations:

5FU - Fluorouracil

DPD/DYPD – dihydropyrimidine dehydrogenase

EMA – European Medicines Agency

FDA – Food and Drug Administration

FEC – Fluorouracil, Epirubicin, Cisplatin

Background

Fluoropyrimidines (5-fluorouracil, capecitabine and the oral prodrug tegafur) are used as the basis of adjuvant and palliative treatment for colorectal, oesophago-gastric, breast and head and neck cancers. In addition, there is increasing use of the same group of drugs in other cancers, including pancreatic cancer and hepato-biliary malignancies. Treatment with fluoropyrimidines is generally well tolerated. However, severe adverse drug reactions have been recognised to occur in 5 – 10% of the treated population.[4,5,6] A significant proportion of adverse drug reactions are likely to be the result of inter-individual genetic variation.

The metabolic pathways by which 5-fluorouracil (5FU) is converted to active nucleotide analogues is well described.[7] Dihydropyrimidine dehydrogenase (DPD, encoded by the *DPYD* gene) inactivates 80-90% of 5FU into 5,6-dihydro-fluorouracil[8] . DPD deficiency is found in 3 – 6% of the population and has been associated with severe toxicity (diarrhoea, neutropenia, mucositis).[9,10,11] Variants in *DPYD* is the best recognised cause of primary deficiency of DPD associated with severe toxicity. The most clinically relevant variants are *DPYD**2A (IVS14+1G>A, c. 1905+ 1G>A, or rs3918290) and c.2846A>T (D949V or rs67376798).[12,13] A meta-analysis has demonstrated that additional *DPYD* variants c. 1679T>G and c.1236G>A/*HapB3DPYD* are clinically relevant predictors of fluoropyrimidine ,toxicity.[14]

On 30th April 2020 the European Medicines Agency recommended patients should be tested for the lack of DPD before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.[2] Scientific groups such as the Clinical Pharmacogenetics Implementation Consortium

and the Dutch Pharmacogenetics Working Group provide updated gene and drug clinical practice guidelines.[3] This group currently recommend a 25 – 50% reduction in dose of 5FU or capecitabine for the first cycles followed by dose titration guided by toxicity in subsequent cycles for those patients with DPD deficiency.

Deenen and colleagues have now provided evidence that supports the implementation of genotypic testing for *DPYD* variants before the administration of the 5FU prodrug, capecitabine.[15] In this study participants heterozygous for the *DPYD* *2A variant were treated with a reduced dose of capecitabine whereas patients without the variant were treated with the standard dose of capecitabine. Although strict dosage rules were not implemented, the initial dose administered to those heterozygous for the variant was 50% of the standard dose. Further dose adjustments were made by the treating physician based on toxicity and experience. Overall, of the 18 participants with *DPYD**2A variant included in the study only 5 (28%) experienced ≥ grade 3 toxicity. This rate is lower than the 70 – 90% of grade ≥3 toxicity previously reported in this population.[15,16] Nonetheless, this report is limited by the limited efficacy data included and absence of long-term follow-up. Lunenburg and colleagues have shown that *DPYD* testing, and pharmacogenomic-directed dosing can be implemented in practice.[17] This study used a model where identified DPD alleles are assigned a score based on the impact on DPD activity. The initial dose administered is based on the total score.[18]

Individuals carrying one decreased function *DPYD* variant (heterozygous) may tolerate higher doses of fluoropyrimidine compared to heterozygous carriers of no function variants.[19] A prospective study by Knikman et al. has shown that *DPYD*-guided dose individualisation of fluoropyrimidines does not negatively impact on progression free, or overall survival in a pooled analysis of *DPYD* variant carriers.[20] However, they note the need for close monitoring and early dose modifications, particularly for carriers of the c.1236G>A variant where dose reductions may negatively affect disease progression if doses are not escalated when patients experience no or minimal toxicity.

Guidance

All patients due to receive fluoropyrimidine based therapy, should have a DPD test prior to starting treatment.

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. In exceptional circumstances where an agreement is made from the consultant that the patient can go ahead without a DPD test, the consultant or pharmacist must document clearly on the chemotherapy prescribing system and, in the patient's, medical record.

All patients being considered for fluoropyrimidine (i.e. capecitabine, 5-fluorouracil, tegafur) based therapy should undergo pre-treatment pharmacogenomic screening for loss of function variants of *DPYD* associated with severe toxicity. The following four variants were highlighted in a review by the EMA[2]:

- c. 1905+ 1G>A, (IVS14+1G>A, or rs3918290) or *DPYD**2A
- c.2846A>T, p.D949V (rs67376798)
- c.1679T>G, p.I560S (rs55886062) or *DYPD**13,
- c.1129-5923C>G, c.1236G>A (rs75017182, HapB3)[(a)]

It is known that there are differences in the prevalence of genetic variation within and between ethnic populations, and furthermore that the four variants highlighted by the EMA are predominantly described in White European populations. [21]
Consensus recommendations from the Association for Molecular Pathology Clinical Practice Committee's Pharmacogenomics Working group have defined a number of additional variants for inclusion in clinical pharmacogenomics assays based on their functional impact and frequency in multiethnic populations amongst other considerations.[22] Emerging evidence linking *DPYD* variants to functional impact may result in updates to commercially available assays and platforms and subsequent phenotype assignment. Variants considered in this guideline have been included based on availability of dosing recommendations linked to assigned activity score.

[a] Note: c.1129-5923C>G is intronic and the likely causal variant of the HapB3 haplotype and should be tested for where possible. Recent evidence has shown that the two HapB3 variants are not in complete linkage disequilibrium as previously thought. In cases where only the c.1236G>A has been tested, "decreased function" can only be inferred by detection of the exonic tag SNP, and in rare cases the causal decreased function variant c.1129-5923C>G may not be present despite having the tag SNP, resulting in a rare risk of false-positive at-risk phenotype assignment.[3]

Ordering a DPD test

Each organisation should ensure there is a clear SOP for requesting a *DPYD* test. Details of the local testing facility should be available and working with the laboratory an end-to-end turnaround time of <5 working days should be aimed for. Written information about *DPYD* testing should be made available for patients, an example patient information leaflet is available from the NHS North West Genomic Medicine Service Alliance.[23]

Interpreting the result and modifying the initial dose

Patients identified as having one or more copies of a loss of function *DPYD* variant should be considered for dose modification of first cycle fluoropyrimidines, or alternative therapy that is not a substrate for DPD, as suggested in Table 1 and Table 2 below. Any *DPYD* test results that fall outside of this guidance should be the subject of multidisciplinary discussion. The absence of a loss of function *DPYD* variant being identified does not preclude fluoropyrimidine-associated toxicity related to other genetic (e.g. rare variants in *DPYD* or other genes) or non-genetic (e.g. renal function, co-morbidities) factors.

Dosing subsequent cycles

- Given that some patients carrying decreased or no function *DPYD* variants can tolerate standard doses; to maintain effectiveness of treatment, dose levels should cautiously be increased subsequently in those patients with no, or acceptable levels of toxicity.
- There is little data around specific increment levels to increase by, but a recommendation would be to take a pragmatic approach and increase by 10-12.5% per cycle assuming no, or clinically acceptable toxicity after two treatment cycles. It is recommended that there are at most two stepwise increments.
- Similarly, doses should be decreased in patients who do not tolerate the starting dose.
- Where a patient has had significant toxicities, but the standard *DPYD* test has shown none of the variants to be present, clinicians should consider referring patients for a further test to detect the presence of less common variants, such as

through the Molecular Genetics of Adverse Drug Reactions study (NIHR CPMS ID: 8630) or ethically approved research routes where possible.[24]

Table 1. Dosing recommendations for *DPYD* heterozygous (single variant) genotypes

Likely Phenotype	Variant allele	Predicted % DPD activity	Recommended dose adjustment
***DPYD* Intermediate Metaboliser (Activity Score 1.0)**	c.[1905+1G>A] **OR** c.[1679T>G]	**50**	Reduce starting dose to 50% of target dose or consider alternate therapy*. If tolerated after the first cycle, titrate dose increases based on toxicity or therapeutic drug monitoring over subsequent cycles to maximum of 75% of target dose
***DPYD* Intermediate Metaboliser (Activity Score 1.5)**	c.[2846A>T] OR c.[1129–5923C>G] OR c.[557A>G]	**50-75**	Reduce start dose to 50% of target dose. If tolerated after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles. If no toxicity is observed at a dose of 75%, a further increment to a maximum of 85% may be possible, but caution is advised.
***DPYD* Normal Metaboliser**	No variants identified	100%	Based on genotype there is no indication to change dose or therapy

Table 2. Dosing recommendations for *DPYD* homozygous and compound heterozygous (two variant) genotypes

Likely Phenotype	Variant allele	Predicted % DPD activity	Recommended dose adjustment
***DPYD* Poor Metaboliser (Activity Score 0)**	c.[1905+1G>A];[1905+1G>A] homozygous OR c.[1679T>G];[1679T>G] homozygous OR c.[190511G>A];[1679T>G] compound heterozygous	**0**	Complete DPD deficiency: **Do not use fluoropyrimidine therapy for any of these genotypes**. Recommend use of raltitrexed or trifluridine/ tipiracil or alternate therapy*
***DPYD* Poor Metaboliser (Activity Score 0.5)**	c.[1905+1G>A];[2846A>T] compound heterozygous OR c.[1905+1G>A]; [1129-5923C>G] compound heterozygous OR c.[1905+1G>A];[557A>G] compound heterozygous OR c.[1679T>G]; [1129-5923C>G] compound heterozygous OR c.[1679T>G];[2846A>T] compound heterozygous OR c.[1679T>G];[557A>G] compound heterozygous	**10-25%**	Avoid use of fluoropyrimidine therapy. Consider alternate therapy*. Recommend use of raltitrexed or trifluridine/ tipiracil or alternate therapy*
***DPYD* Intermediate Metaboliser**	c.[557A>G];[557A>G] homozygous	**30-50%**	Reduce starting dose to 50% of

(Activity Score 1.0)	OR c.[1129–5923C>G];[557A>G] compound heterozygous OR c.[2846A>T];[557A>G] compound heterozygous OR c.[1129–5923C>G];[1129–5923C>G] homozygous OR c.[1129–5923C>G];[2846A>T] compound heterozygous OR c.[2846A>T];[2846A>T] homozygous		target dose or consider alternate therapy*. If tolerated after the first cycle, titrate dose increases based on toxicity or therapeutic drug monitoring over subsequent cycles to maximum of 75% of target dose

* The choice of dose reduced fluoropyrimidine or alternate therapy will be informed by the tumour type, clinical indication and predicted severity of enzyme deficiency based on *DPYD* genotype. When alternative therapy is recommended the suggested alternate therapy (raltitrexed or trifluridine/tipiracil) is appropriate where the treating oncologist considers the inclusion of an anti-metabolite the optimal therapeutic option. It is beyond the scope of this guideline to state the appropriate decision for each indication.

For compound heterozygous or homozygous genotypes, the effect of the variant alleles on dose reduction is additive.

Version Control

Version number	Authors	Changes	Date
1	Dr Paul Ross, Dr Tony Marinaki,	n/a	July 2020
2	Dr Paul Ross Jessica Keen Prof Munir Pirmohamed	Addition of c.557 variant and information about prevalence of variation across populations Additional detail on HapB3 haplotype Dosing tables updated to include likely phenotype. Dosing recommendations aligned with CPIC. Clarity on dose titration in “dose modifications section”	Sept 2024

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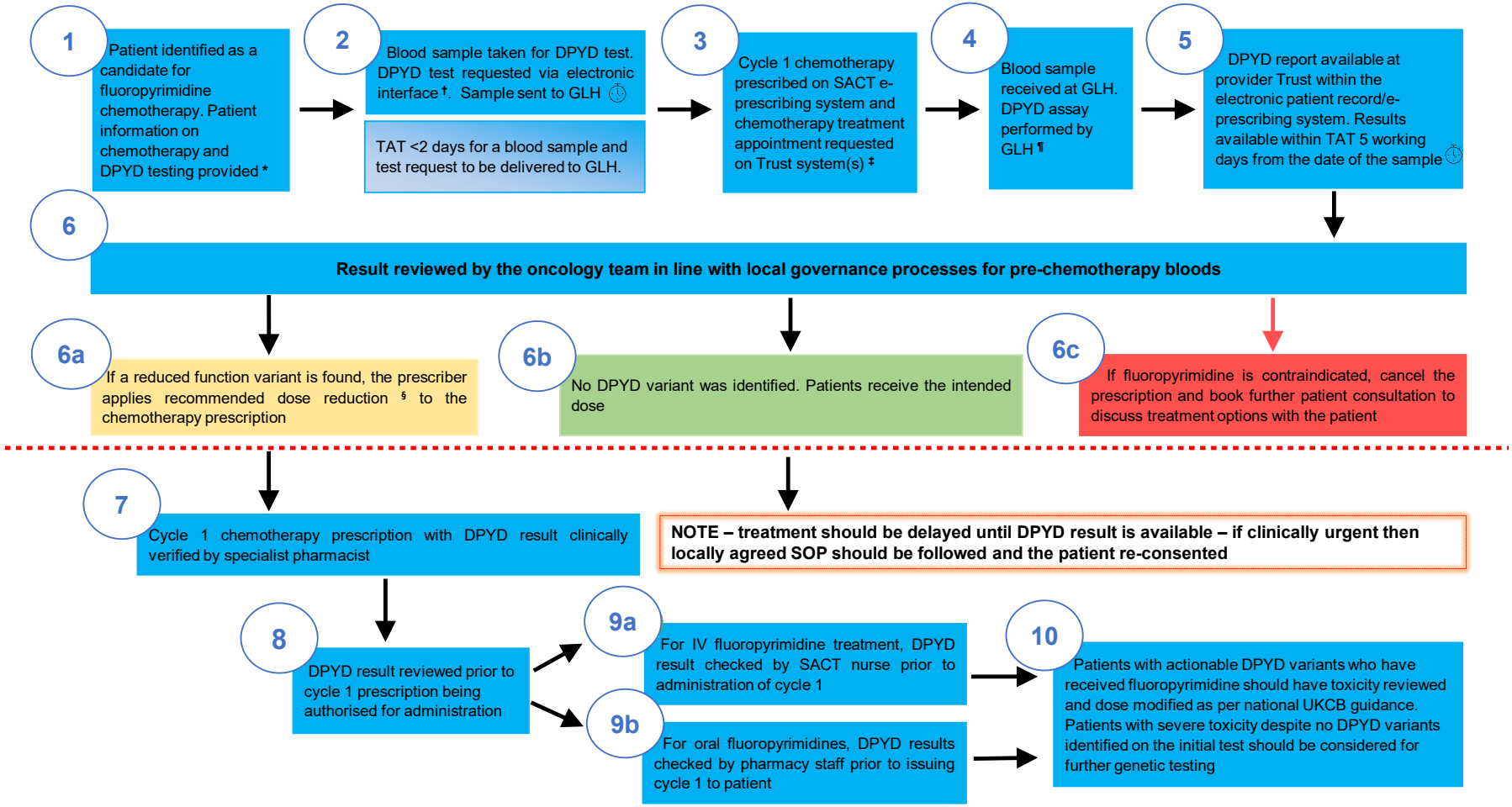
Appendix 1: *DPYD* Best Practice Pathway



Notes on *DPYD* Best Practice Pathway

Prescribers include but are not limited to: Consultant Oncologist, Registrar/Clinical Fellow, Independent Prescribers and Non-medical prescribers.

***** Detailed written information on *DPYD* testing e.g. patient information leaflets or websites, should be made available for patients in support of information delivered verbally by the oncology team. Information on *DPYD* testing should be given along with chemotherapy information sheets.

† The GMSA/ National Project team recognise that the infrastructure permitting *DPYD* tests to be requested and reported to and from EPR and order-comms systems is not currently in place in provider organisations, including those with embedded GLHs. All providers will need to introduce systems capable of interoperability to allow such system-to-system communication and implement information and data standards (that will be developed nationally). This will allow standardised working across a number of genomic tests as well as audit and improving visibility of results within provider systems.

‡ Ideally prescribing of fluoropyrimidines would be carried out only after a patient's pre-emptive *DPYD* result has been reported, however the Gold Standard Pathway allows for fluoropyrimidine prescribing in advance of *DPYD* testing to reflect the practicalities of service provision where the majority of patients will not have an actionable *DPYD* variant. Each Trust should have a standard operating procedure for the responsibility of all healthcare professionals checking the *DPYD* results in this pathway before chemotherapy is given to the patient.

¶ All testing should be done by the GLH (or approved lab via SLA). GLH turnaround time (TAT) should be <3 days.

6. For patients with actionable results (6a and 6c) oncology teams should return these results to the patient and discuss the impact of their genetic result on their individual treatment, providing further written information as needed by the patient. Patients with no variant identified (6b) may still wish to know their result and providers should offer this information at an early opportunity during the treatment course.

§ Recommended dose reduction from report/ recommended dose reduction based on UK Chemotherapy board national guidance/ local guidance. UK Chemotherapy Board. (2020). Personalised Medicine Approach for Fluoropyrimidine-based Therapies. Accessed at: https://www.theacp.org.uk/userfiles/file/resources/dpd-testing-ukcb-july-2020-final.pdf

NHS North West Genomic Medicine Service Alliance,
NHS East Genomic Medicine Service Alliance,
NHS North Thames Genomic Medicine Service Alliance,
NHS South East Genomic Medicine Service Alliance

NHS North East and Yorkshire Genomic Medicine Service Alliance,
NHS Central and South Genomic Medicine Service Alliance,
NHS South West Genomic Medicine Service Alliance