LABORATORY REPORT

Patient Name:	DUMMY	**Booking ID:**	NA
Age:	NA	**Sample Type:**	NA
Gender:	NA	**Sample Collection Date:**	DD-MM-YYYY
Referring Clinician:	NA	**Sample Receiving Date:**	DD-MM-YYYY
Test Requested:	*Dihydropyrimidine Dehydrogenase (DPYD) Mutation Analysis by PCR, Sanger Seq.*	**Reporting Date:**	DD-MM-YYYY

Dihydropyrimidine Dehydrogenase (DPYD) Mutation Analysis

CLINICAL INFORMATION

N/A

RESULTS

***DPYD,* NM_000110.3 Variants**	**dbSNP**	**Mutation status**	**Interpreatation**
DPYD *2A, IVS14+1 G>A, c.1905+1G>A	rs3918290	Homozygous Normal	Wild Type Allele
DPYD *13, c.1679T>G	rs55886062	Homozygous Normal	Wild Type Allele
DPYD, c.2846A>T	rs67376798	Homozygous Normal	Wild Type Allele

DETAILED RESULT INFORMATION

There is absence of DPYD target based gene mutations in the specimen received. No variants detected in DPYD: predictive of *1 functional alleles.

Genotype classification	**Dosage recommendation**
Homozygous Allele	Avoid 5FU. Select alternate drug
Heterozygous Allele	Reduce the starting dose by 50%, followed by dose titration based on clinical judgement (and ideally therapeutic drug monitoring)
Wild-type Allele	No Indication to change the dose or therapy

CLINICAL INTERPRETATION

- ✓ Please correlate clinically.
- ✓ The DPYD wild-type allele is associated with normal enzyme activity.
- ✓ Individuals who are heterozygous with one altered function DPYD allele are DPYD intermediate metabolizers.
- ✓ Individuals who have 2 non-functional DPYD alleles are DPYD poor metabolizers.
- ✓ Results should be interpreted in context of clinical findings, relevant history, and other laboratory data.

898 898 1777 care@redcliffelabs.com www.redcliffelife.com

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COMMENTS

- ✓ Fluorouracil, or 5-flourouracil (5-FU), is a chemotherapy agent that belongs to the drug class of fluoropyrimidines.
- ✓ 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.
- ✓ Please refer to The FDA Drug Label for Fluorouracil: Warning DPD Deficiency (2020).
- ✓ The analytical sensitivity of the assay is 0.51 ng/µl and analytical specificity of the assay is 100%

TEST DESCRIPTION

This DPYD gene mutation detection is a PCR and Sanger Sequencing technique based diagnostic test designed to detect mutations present at predefined nucleotide position in DPYD gene in DNA extracted from whole blood. This test was developed and its analytical performance characteristics have been determined by Redcliffe labs. It has not been cleared or approved by FDA.

TEST LIMITATIONS

- ✓ This test is performed on PCR followed by Sanger Sequencing. The analytical sensitivity of the test allows detection of the mutation when the mutant is at least 18-20%.
- ✓ Test is DNA based, samples must be received at the laboratory under cool-pack conditions (4-8 ℃) within 72 hrs of collection to ensure preservation of intact DNA.
- ✓ Test results may vary if appropriate sample collection and transportation to lab not followed as per protocol.
- ✓ This test is laboratory developed and its performance were evaluated at Redcliffe Labs.
- ✓ Mutations below the detection limits of the assay may not be detected. Typical detection limit for Sanger Sequencing assays is >10-20%.
- ✓ This test detects only the NM_000110.3:c.2846A>T, c.1905+1G>A, c.1679T>A variants in the DPD gene. Other mutations are not detected by this test.
- ✓ This report only includes variants that meets a level of evidence threshold for cause or contribute to disease.
- ✓ Gene transcript used for clinical reporting generally represents the canonical transcript, which is usually the longest coding transcript with strong/multiple supporting evidence.

DISCLAIMER

- ❖ Test has been performed assuming that the sample received belongs to the above-named individual(s) and that any stated relationships between individuals are accepted as true.
- ❖ This test is performed using a in house developed kit. The assay is designed to perform the reactions at the specified analytical sensitivity given that the template DNA is not heavily fragmented, and does not contain materials that could inhibit the amplification reaction.
- ❖ This assay will only screen the DPYD:c.1905+1G>A (rs3918290), c.1679T>G and c.2846A>T genotype. Genetic and/or non genetic factors not detected by this test may affect 5-FU drug metabolism, efficacy and risk for toxicity.
- ❖ Genotyping does not replace the need for therapeutic drug monitoring or clinical observation. Lack of detection of the targeted DPYD variant does not rule out risk for 5-FU toxicity or predict degree of responsiveness to 5-FU. Diagnostic errors can occur due to rare sequence variations.
- ❖ The results should be interpreted in the context of the patient's medical evaluation. Mutation identified in this gene does not guarantee activity of the drug in a given indication due to presence of contraindicated mutation in gene.
- ❖ The mutation information provided should only be utilized as a guide or aid and the decision to select any therapy option based on the information reported here resides solely with the discretion of the treating physician.
- ❖ This report should only be used as an aid and the treating physician should employ sound clinical judgment in arriving at any decision for patient care or treatment.

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REFERENCE

1. FLUOROURACIL - fluorouracil injection, solution [package insert]. Illinois, USA: FreseniusKabi; 2020. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c45f5286-a52b-43e5-8a6f-d0312e7da0c8
2. Amstutz U., Henricks L.M., Offer S.M., Barbarino J., et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210 –216.
3. Lunenburg C., van der Wouden C.H., Nijenhuis M., Crommentuijn-van Rhenen M.H., et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet. 2020;28(4):508–517.
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5. Wilson P.M., Danenberg P.V., Johnston P.G., Lenz H.J., et al. Standing the test of time: targeting thymidylate biosynthesis in cancer therapy. Nat Rev Clin Oncol. 2014;11(5):282–98.

.....End of Report.....

Disclaimer: Method given in report are only indicative and can be changed depending upon type of machine and kit available at time of testing.

Not all tests at all locations are under NABL scope. Availability of tests under NABL scope varies from lab to lab.

Analyzed & Reviewed by
Imran Haider
Senior Scientific Officer
Onco-Genomics

Approved by
Dr. Himani Pandey
Postdoc-SGPGIMS Lucknow
Lab Head-Clinical Genomics

898 898 1777 care@redcliffelabs.com www.redcliffelife.com
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2. It is to be presumed that the tests performed pertain to the specimen/sample attributed to the Customer's name or identification. It is presumed that the verification particulars have been cleared out by the customer or his/her representation at the point of generation of said specimen / sample. It is hereby clarified that the reports furnished are restricted solely to the given specimen only.

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