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**MEDGENOME**

## DNA TEST REPORT – MEDGENOME LABORATORIES

|                      |                                                                   |                                  |                      |
|----------------------|-------------------------------------------------------------------|----------------------------------|----------------------|
| Full Name/ Ref No:   | Mr. Lebbe                                                         | Order ID/ Sample ID:             | 1468372/9434173      |
| Date of Birth / Age: | 69 years                                                          | Gender:                          | Male                 |
| Referring Clinician: | Dr. Mahilal Wijekoon,<br>Aegle Omics Private Limited -<br>Colombo | Specimen Type:                   | EDTA blood (3 tubes) |
|                      |                                                                   | Date of Sample Collection:       | 30-09-2025           |
| Date of Order:       | 03-10-2025                                                        | Date and time of sample receipt: | 03-10-2025; 01:40 PM |
| Test Requested:      | DPYD mutation analysis (MGM340)                                   | Date and time of report:         | 16-10-2025; 02:23 PM |

## CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

The subject is presented with moderately differentiated invasive adeno carcinoma and thus has been tested for variation in the *Dihydropyrimidine dehydrogenase (DPYD)* gene for Fluorouracil (5-FU) drug sensitivity.

## RESULTS

**c.85T>C (\*9A) [One copy] – NORMAL FUNCTION ALLELE HAS BEEN IDENTIFIED IN THE *DPYD* GENE**

**NORMAL METABOLIZER**

| Gene | Allele        | Zygosity     | Allele function <sup>#</sup> |
|------|---------------|--------------|------------------------------|
| DPYD | c.85T>C (*9A) | Heterozygous | Normal function              |

<sup>#</sup> - Allele function is according to The Clinical Pharmacogenetics Implementation Consortium (CPIC).

## VARIANT INTERPRETATION AND RECOMMENDATION

Variant c.85T>C (\*9A) [One copy] was detected in *DPYD* gene in this subject (Ref. Appendix). This allele is assigned to normal function according to CPIC DPYD allele functionality reference.<sup>[1]</sup> The individual tested here has Normal DPD activity and “normal” risk for fluoropyrimidine toxicity. **According to CPIC guidelines there is no indication to change dose or therapy and recommends to follow label recommended dosage and administration.**<sup>[1]</sup> Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy. All changes in medications must be done under clinical supervision.

## BACKGROUND INFORMATION

*DPYD* (OMIM\*612779) gene encodes Dihydropyrimidine dehydrogenase (DPD), a rate limiting enzyme in pyrimidine catabolism. In the liver, DPD is known to degrade 85% of most frequently prescribed anticancer drug 5-FU, thus limiting the amount of drug available for conversion into active metabolites. Various clinical studies across the globe, have established that approximately 40-60% of cancer patients who are DPD deficient develop severe life threatening 5-FU toxicities. However, 5-FU is generally well tolerated at standard doses. The *DPYD* variants can lead to a decreased enzyme activity and hence increase the risk for 5-FU toxicity. <sup>[1, 2]</sup> Till date, more than 30 *DPYD* variations have been reported, of which some of them are clearly linked to 5-FU toxicity e.g., IVS14+1G>A point variation. Genetic screening of cancer patients for the presence of *DPYD* variations before the administration of 5-FU is appropriate in order to prevent lethal 5-FU-related toxicity.

## METHODOLOGY

Targeted gene sequencing: Genomic DNA was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >80- 100X coverage on Illumina sequencing platform. We follow the GATK best practices framework for identification of variants in the sample using Sentieon (v201808.07). <sup>[3]</sup> The sequences obtained are aligned to human reference genome (GRCh38.p13) using Sentieon aligner <sup>[3, 4]</sup> and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels. <sup>[3]</sup> Sentieon haplotype caller has been used to identify variants which are relevant to the clinical indication. Gene annotation of the variants is performed using VEP program <sup>[5]</sup> against the Ensembl release 99 human gene model. <sup>[6]</sup>

## GUIDELINES FOR CLINICAL INTERPRETATION

The Clinical Pharmacogenetics Implementation Consortium (CPIC) <sup>[7]</sup> is an international consortium that facilitates clinical implementation of pharmacogenetic tests through published gene/drug clinical practice guidelines. CPIC clinical guidelines are endorsed by American Society of Health-System Pharmacists (ASHP) and American Society for Clinical Pharmacology and Therapeutics (ASCPT). This Pharmacogenomic test has been assessed based on recommendations of the Clinical Pharmacogenetics Implementation Consortium, CPIC, as updated on April 2025. Gene and disease coverage will change as per recommendations and research advancements/reports.

## LIMITATIONS

- Only CPIC recommended alleles in *DPYD* are assayed in this test.
- Genetic testing is highly accurate. Rarely, inaccurate results may occur for various reasons. These reasons include, but are not limited to: mislabeled samples, inaccurate reporting of clinical/medical information, rare technical errors or unusual circumstances such as bone marrow transplantation, blood transfusion; or the presence of change(s) in such a small percentage of cells that may not be detectable by the test (mosaicism).

## DISCLAIMER

- Interpretation of variants in this report is performed to the best knowledge of the laboratory based on the information available at the time of reporting. The classification of variants can change over time and MedGenome cannot be held responsible for this. Please feel free to contact MedGenome Labs (techsupport@medgenome.com) in the future to determine if there have been any changes in the classification of any variations. Re-analysis of variants in previously issued reports in light of new evidence is not routinely performed but may be available upon request.

- Very rarely in spite of having normal report, absence of toxicity cannot be guaranteed because of other rare genetic variations present in DPYD gene and which are not recommended by CPIC.
- The variations have not been validated/confirmed by Sanger sequencing.
- The report shall be generated within agreed turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MedGenome under no circumstances will be liable for any delay beyond afore mentioned TAT.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MedGenome hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MedGenome hereby disclaims all liability arising in connection with the report(s).
- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MedGenome. In case where any test provided by MedGenome fails for unforeseeable or unknown reasons that cannot be influenced by MedGenome in advance, MedGenome shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognised by MedGenome in advance.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by MedGenome.



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## REFERENCES

1. Amstutz U, *et al.*, (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.*, 103:210-216.
2. Diasio RB, *et al.*, (1988). Familial deficiency of dihydropyrimidine dehydrogenase. Biochemical basis for familial pyrimidinemia and severe 5- fluorouracil-induced toxicity. *J Clin Invest.*, 81:47-51.
3. Freed D, *et al.*, (2017). The Sentieon Genomics Tools-A fast and accurate solution to variant calling from next-generation sequence data. *BioRxiv.*, 115717.
4. Li H, *et al.*, (2010). Fast and accurate long-read alignment with Burrows-Wheeler transform. *Bioinformatics.*, 26:589-595.
5. McLaren W, *et al.*, (2010). Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. *Bioinformatics.*, 26:2069-2070.
6. Zerbino D, R. *et al.*, (2018). Ensembl 2018. *Nucleic Acids Res.* 46:D754-D761.
7. CPIC: <https://cpicpgx.org/>

**APPENDIX: LIST OF *DPYD* ALLELES COVERED IN THE PANEL**

| Sl. No | ALLELES COVERED | ALLELE FUNCTION    | Sl. No | ALLELES COVERED | ALLELE FUNCTION    |
|--------|-----------------|--------------------|--------|-----------------|--------------------|
| 1      | *10             | No function        | 22     | c.1278G>T       | Normal function    |
| 2      | *11             | Normal function    | 23     | c.1294G>A       | Normal function    |
| 3      | *12             | No function        | 24     | c.1314T>G       | Decreased function |
| 4      | *13             | No function        | 25     | c.1349C>T       | Normal function    |
| 5      | *2A             | No function        | 26     | c.1358C>G       | Normal function    |
| 6      | *3              | No function        | 27     | c.1371C>T       | Normal function    |
| 7      | *4              | Normal function    | 28     | c.1403C>A       | Normal function    |
| 8      | *5              | Normal function    | 29     | c.1475C>T       | No function        |
| 9      | *6              | Normal function    | 30     | c.1484A>G       | No function        |
| 10     | *7              | No function        | 31     | c.1519G>A       | Normal function    |
| 11     | *8              | No function        | 32     | c.1543G>A       | Normal function    |
| 12     | *9A             | Normal function    | 33     | c.1577C>G       | Normal function    |
| 13     | *9B             | Normal function    | 34     | c.1615G>A       | Normal function    |
| 14     | c.1024G>A       | No function        | 35     | c.1682G>T       | Normal function    |
| 15     | c.1057C>T       | No function        | 36     | c.1774C>T       | No function        |
| 16     | c.1108A>G       | Normal function    | 37     | c.1775G>A       | No function        |
| 17     | c.1129-5923C>G  | Decreased function | 38     | c.1777G>A       | No function        |
| 18     | c.1180C>T       | Normal function    | 39     | c.1796T>C       | Normal function    |
| 19     | c.1181G>T       | Normal function    | 40     | c.1896T>C       | Normal function    |
| 20     | c.1218G>A       | Normal function    | 41     | c.1905C>G       | Normal function    |
| 21     | c.1260T>A       | Normal function    | 42     | c.1906A>C       | Normal function    |



| Sl. No | ALLELES COVERED | ALLELE FUNCTION    | Sl. No | ALLELES COVERED                         | ALLELE FUNCTION    |
|--------|-----------------|--------------------|--------|-----------------------------------------|--------------------|
| 43     | c.1990G>T       | Normal function    | 63     | c.3049G>A                               | Normal function    |
| 44     | c.2021G>A       | No function        | 64     | c.3061G>C                               | Normal function    |
| 45     | c.2161G>A       | Normal function    | 65     | c.3067C>A                               | Normal function    |
| 46     | c.2186C>T       | Normal function    | 66     | c.313G>A                                | Normal function    |
| 47     | c.2195T>G       | Normal function    | 67     | c.343A>G                                | Normal function    |
| 48     | c.2279C>T       | Decreased function | 68     | c.451A>G                                | Normal function    |
| 49     | c.2303C>A       | Normal function    | 69     | c.46C>G                                 | Normal function    |
| 50     | c.2336C>A       | Normal function    | 70     | c.496A>G                                | Normal function    |
| 51     | c.2482G>A       | Normal function    | 71     | c.498G>A                                | Normal function    |
| 52     | c.2582A>G       | Normal function    | 72     | c.525G>A                                | Normal function    |
| 53     | c.2623A>C       | Normal function    | 73     | c.557A>G                                | Decreased function |
| 54     | c.2639G>T       | No function        | 74     | c.601A>C                                | No function        |
| 55     | c.2656C>T       | Normal function    | 75     | c.61C>T                                 | No function        |
| 56     | c.2846A>T       | Decreased function | 76     | c.62G>A                                 | Normal function    |
| 57     | c.2872A>G       | No function        | 77     | c.632A>G                                | No function        |
| 58     | c.2915A>G       | Normal function    | 78     | c.868A>G                                | Decreased function |
| 59     | c.2921A>T       | Normal function    | 79     | c.929T>C                                | Normal function    |
| 60     | c.2933A>G       | No function        | 80     | c.934C>T                                | Normal function    |
| 61     | c.2977C>T       | Normal function    | 81     | c.967G>A                                | Normal function    |
| 62     | c.2978T>G       | Normal function    | 82     | c.1129-5923C>G,<br>c.1236G>A<br>(HapB3) | Decreased function |

-----End of report-----