Pharmacogenetic Testing for Fluoropyrimidines at Instituto Nacional de Câncer, Brazil

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The present letter focuses on the pharmacogenetic (PGx) testing of variants of the *dihydropyrimidine dehydrogenase* (*DPYD*) gene available at Instituto Nacional de Câncer (INCA), Rio de Janeiro, for cancer patients who are candidates for treatment with the fluoropyrimidines 5-fluorouracil (5-FU) and/or capecitabine.[1] The rationale for *DPYD* genotyping is as follows: *DPYD* encodes the enzyme dihydropyrimidine dehydrogenase (DPD), which accounts for approximately 85% of 5-FU elimination in humans; consequently, reduction in or absence of DPD activity due to reduced or no-function *DPYD* variants leads to 5-FU accumulation and increased risk of toxicity. This also affects patients treated with capecitabine, since 5-FU is capecitabine's active metabolite.

The original *DPYD* genotyping panel adopted at INCA assessed 4 single-nucleotide polymorphisms (SNPs) listed in the Clinical Pharmacology Implementation[2] (CPIC) and the Dutch Pharmacogenomic Working Group[3] (DWPG) guidelines, namely rs391820 (*DPYD**2A), rs55886062 (*DPYD***13*), rs56038477, and rs67376798. After genotyping 230 patients, we reported minor allele frequencies (MAFs) of rs391820, rs67376798, and rs56038477, similar to other Brazilian cohorts,[4,5] whereas rs55886062 was consistently absent.[6]

Based on these data and on the current structure of the Brazilian population,[7] our *DPYD* genotyped panel was updated by replacing rs55886062 with rs115232898, a reduced-function SNP,[8] tightly linked to African ancestry, listed among the Tier-1 variants in the Joint Consensus for *DPYD* genotyping recommendations.[9] As the present letter is written, 285 patients have been genotyped at INCA for rs115232898 and 4 were heterozygous for the variant T allele (MAF = 0.74%); of notice, these 4 patients self-identified as Black (*Preto*, in Portuguese), according to the race/skin color classification of the Brazilian Census.

At MAF = 0.74%, rs115232898 was the second most common SNP of the *DPYD* genotyping panel; only rs56038477 was detected at a higher MAF (1.07%) in our cohort. The rs56038477 SNP is commonly used to identify the reduced-function *DPYD HapB3* haplotype, based on the assumption of its complete linkage disequilibrium (LD) with rs75017182 (c.1129–5923C > G), which defines the *HapB3* haplotype. However, a recent report[10] of incomplete, albeit extensive (D' = 0.985) LD between these two SNPs prompted the suggestion that, in rare cases, the recommendation for reduced fluoropyrimidine dosing, based on the rs56038477 genotype, would be inappropriate and could negatively impact the drug response. This concern led us to genotype rs75017182 in all patients who had received fluoropyrimidine dosing recommendations based on the rs56038477 genotype. This analysis verified a perfect LD between the two SNPs: the 6 patients heterozygous for rs56038477 were also carriers of rs75017182 in heterozygosis, whereas all other patients had the reference allele in homozygosis at both loci. Perfect LD of these two SNPs in Brazilians may also be inferred from their identical MAF (0.43%) in a large, admixed cohort of elderly individuals.[11]. Thus, we feel confident about fluoropyrimidine dosing recommendations based on rs56038477 as a surrogate marker for *DPYD HapB3*.

Collectively, the genotyping panel for the 4 SNPs (rs391820, rs55886062, rs56038477, and 115232898) currently in use at INCA identified 10 patients as carriers of 1 of the reduced or no-function *DPYD* alleles, plus 1 patient heterozygous for rs3918290 and rs56038477. These patients were assigned the intermediate (IM; $N = 10$; frequency: 3.5%) and the poor DPD metabolizer phenotype (PM; $N = 1$; frequency: 0.4%) respectively, and received recommendations for fluoropyrimidine initial dosing according to the CPIC[2] and DWPG[3] guidelines. These data were then used to predict the diagnostic performance of 12 commercial laboratories offering *DPYD* tests in Brazil, identified through

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an internet search.[12] Five of these laboratories genotype all SNPs in our panel; thus, they are expected to reproduce our results. By contrast, the other 7 laboratories do not include rs56038477 nor rs115232898 in their genotyping panels and would misclassify 9 of the 10 IMs as normal metabolizers (NMs), and, most importantly, misclassify the high-risk PM patient as IM. This high rate of misclassification (90.9%) derives from the fact that the missing rs56038477 and rs115232898 SNPs are the most prevalent in our patient cohort, as aforementioned. This analysis extends to Brazilian patients the reported concerns regarding the limitations and variability in *DPYD* variant detection by commercial laboratories in the United States, and the potential deleterious impact on PGx-informed dosing recommendations for fluoropyrimidines.[13]

In conclusion, the implementation and updating of PGx testing of *DPYD* variants at INCA conforms to the requirement/recommendation by several drug regulatory agencies (such as the European Medicines Agency [EMA], the United States Food and Drug Administration [FDA], and Health Canada/Santé Canada [HSCS]) for *DPYD* genotyping prior to fluoropyrimidine administration.[14] Accordingly, the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA, in Portuguese) package insert for capecitabine states that "the test for DPD deficiency should be considered according to the local availability and current guidelines."[15] However, the package insert for 5FU[16] makes no reference to *DPYD* or DPD testing.

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Conflict of Interests
The author has no conflict of interests to declare.

References

1 Suarez-Kurtz G. Pharmacogenomic tests of oncology drugs at Instituto Nacional de Câncer (INCA). Braz J Oncol 2021;17:e-20210010. Doi: 10.5935/2526-8732.20210010
2 Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, J Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther 2018;103(02):210–216. Doi: 10.1002/cpt.911
3 Lunenburg CATC, Van der Wouden CH, Nijenhuis M, Crommentuijn-van Rhenen MH, De Boer-Veger NJ, Buunk AM, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet 2020;28(04):508–517. Doi: 10.1038/s41431-019-0540-0
4 Naslavsky MS, Scliar MO, Yamamoto GL, Wang JYT, Zverinova S, Karp T, et al. Whole-genome sequencing of 1,171 elderly admixed individuals from São Paulo, Brazil. Nat Commun 2022;13(01):1004. Doi: 10.1038/s41467-022-28648-3
5 Botton MR, Hentschke-Lopes M, Matte U. Frequency of DPYD gene variants and phenotype inference in a Southern Brazilian population. Ann Hum Genet 2022;86(02):102–107. Doi: 10.1111/ahg.12453
6 Suarez-Kurtz G, Fernandes VC, Elias ABR. Implementation of DPYD genotyping in admixed American populations: Brazil as a model case. Clin Pharmacol Ther 2023;114(01):23–24. Doi: 10.1002/cpt.2921
7 Pena SD, Di Pietro G, Fuchshuber-Moraes M, Genro JP, Hutz MH, Kehdy FdSG, et al. The genomic ancestry of individuals from different geographical regions of Brazil is more uniform than expected. PLoS One 2011;6(02):e17063. Doi: 10.1371/journal.pone.0017063
8 Suarez-Kurtz G. DPYD genotyping panels: Impact of population diversity. Clin Transl Sci 2024;17(04):e13805. Doi: 10.1111/cts.13805
9 Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, et al. DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. J Mol Diagn 2024;26(10):851–863. Doi: 10.1016/j.jmoldx.2024.05.015
10 Turner AJ, Haidar CE, Yang W, Boone EC, Offer SM, Empey PE, et al. Updated DPYD HapB3 haplotype structure and implications for pharmacogenomic testing. Clin Transl Sci 2024;17(01):e13699. Doi: 10.1111/cts.13699
11 Arquivo Brasileiro Online de Mutações (AbraOM) [Internet]. São Paulo: Centro de Estudos do Genoma Humano e Células-Tronco/Universidade de São Paulo. Available from: https://abraom.ib.usp.br/search.php
12 Suarez-Kurtz G. Letter to the Editor: Variant Coverage and Diagnostic Performance of Commercially Available DPYD Genotyping Tests in Brazil. J Natl Compr Canc Netw 2024;22(08):e247059. Doi: 10.6004/jnccn.2024.7059
13 Nguyen DG, Morris SA, Chen A, Moore DC, Hanson SL, Larck C, et al. Unveiling Discrepant and Rare Dihydropyrimidine Dehydrogenase (DPYD) Results Using an In-House Genotyping Test: A Case Series. J Natl Compr Canc Netw 2024;22(04):e247022. Doi: 10.6004/jnccn.2024.7022
14 Pharmacogenomics Knowledge Base (PharmGKB) [Internet]. Stanford (CA): Stanford University. Available from: https://www.pharmgkb.org/labelAnnotations
15 Agência Nacional de Vigilância Sanitária (ANVISA). Xeloda [Internet]. Brasília: ANVISA. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=XELODAhttps://abraom.ib.usp.br/search.php
16 Agência Nacional de Vigilância Sanitária (ANVISA). Fluoruracila [Internet]. Brasília: ANVISA. Available from: https://consultas.anvisa.gov.br/#/bulario/?nomeProduto=FLUORURACILA

