Predicting life-threatening fluoropyrimidine toxicity beyond *DPYD* testing

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Pharmacodynamics of fluoropyrimidines (FP) potentially depends on polymorphisms of genes related to its catabolism, anabolism, folate pathways, its targets and transporters. Before starting FP-based chemotherapy, the European Medicines Agency (EMA) and the Clinical Pharmacogenetic Implementation Consortium (CPIC) recommend testing of 4 variants of the DPYD gene coding for the dihydropyrimidine dehydrogenase (DPD) enzyme, and subsequent FP dose reduction in variant carriers. However, the literature shows that these 4 DPYD variants are carried by only 7% of Caucasians explaining at best 20-30% of early FP-related severe toxicities. So, to improve current recommendations, FUSAFE2 international consortium aims at identifying a multigenic signature by sequencing the entire DPYD gene, 18 MIR genes, 185 additional pharmacogenes potentially relevant for FP, oxaliplatin, irinotecan and cetuximab pharmacodynamics. While expecting final results on the whole targeted pharmacogenes, we herein present a prediction model for G4-5 toxicities based on clinical covariates and expanded *DPYD* genotype. The online calculator ((https://fluoropyrimidine-toxicity-predictor.gustaveroussy.fr/) subsequently developed allows an estimation of the individual probability of developing severe toxicity. By using this new tool, clinicians could better manage the FP-related severe toxicities in clinical routine.