Genotype-guided fluoropyrimidine dosing: ready for implementation

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The impact of genetic variation in the dihydropyrimidine dehydrogenase gene (DPYD) on the individual risk of severe toxicity from chemotherapy with fluoropyrimidines was first described over twenty years ago. However, the clinical benefits of genotype-guided fluoropyrimidine dosing have only recently been demonstrated in prospective studies. Here, an overview over the discovery and replication of associations between four key DPYD risk variants and fluoropyrimidine-related toxicity will be presented together with the most recent evidence-based clinical practice recommendations for genotype-guided dosing, evidence from studies evaluating the implementation of prospective DPYD testing, and a discussion of combining DPYD testing with therapeutic drug monitoring for further therapy optimization and individualization. Used initially as a textbook example of a pharmacogenetic syndrome during the early days of pharmacogenetic research, DPYD testing in patients receiving fluoropyrimidine-based chemotherapy now indeed serves as one of only few examples for a pharmacogenetic test related to drug metabolism that is gaining uptake in clinical practice.