DPYD genotype-guided dose individualisation of fluoropyrimidine therapy: who and how?

We read the Article by Linda Henricks and colleagues[1] with interest and congratulate them for their success in completing a rigorous, multicentre study that showed the feasibility of *DPYD* screening before fluoropyrimidine treatment to reduce fluoropyrimidine-related toxicity. Although we agree, in principle, with the authors that "implementation of *DPYD* genotype-guided individualised dosing should be a new standard of care", there are still unresolved issues with this approach.

In the study, patients were genotyped before the start of fluoropyrimidine therapy for the four specified *DPYD* variants. Non-carriers of these variants were considered to be wild-type patients. Although severe toxicities in the carriers of *DPYD* variants were less frequent than in the historical cohort, there were still 23% grade 3 or worse adverse events in wild-type patients in the study by Henricks and colleagues. Although there might be confounders, such as patient condition and chemotherapy partner to fluoropyrimidine, it would be reasonable to assume that a proportion of these wild-type patients might carry variants that were not detectable by the method of genotyping used by Henricks and colleagues. We advocate full sequencing of the *DPYD* gene instead of the usual genotyping approach, because this means novel deleterious *DPYD* variants can be found.[2] Sequencing, followed by measurement of enzymatic activity in case of a novel variant, should be feasible, with short turnaround time and affordable cost in the light of potentially severe toxicity.

The pharmacokinetic data from the study by Henricks and colleagues suggested that there was adequate drug exposure in the variant carriers with genome-guided dose individualisation. However, drug exposure should not be automatically regarded as equivalent to clinical outcomes and patient survival, which were not reported by Henricks and colleagues. Last, but not least, there are known regional differences in the tolerability profiles of fluoropyrimidines, with tolerability being the best in east Asia and the worst in the USA; however, the exact reason for these differences has not been fully deciphered because of the paucity of *DPYD* genotyping data in Asia.[3,4] Indeed, Henricks and colleagues recruited mainly white participants, with only 2% of participants being Asian in origin. There is an unmet need for a similar study in an Asian population to better inform the feasibility and generalisability of the such an approach in Asia.

The authors' findings reaffirmed the role of *DPYD* screening and suggested the potential benefit of genotype-guided dose individualisation of fluoropyrimidine therapy. Future studies should investigate the optimal genotype platform, report clinical outcomes, and incorporate data from peopel of different ethnic origin.

We declare no competing interests.

*Ka On Lam, Chi Chung Tong, Victor Ho Fun Lee, Mai Yee Luk, Ching Wan Lam
lamkaon@hku.hk

Department of Clinical Oncology (KOL, VHFL) and Department of Pathology (CWL), Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Special Administrative Region, China; Department of Clinical Oncology, Queen Mary Hospital, Hong Kong, Special Administrative Region, China (KOL, CCT, VHFL, MYL); and Clinical Oncology Centre, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China (KOL, VHFL)

1 Henricks LM, Lunenburg CATC, de Man FM, et al. *DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol* 2018; **11:** 1459–67.
2 Tong CC, Lam CW, Lam KO, Lee VHF, Luk MY. A novel *DPYD* variant associated with severe toxicity of fluoropyrimidines: role of pre-emptive *DPYD* genotype screening. *Front Oncol* 2018; **8:** 279.
3 Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 2008; **26:** 2118–23.
4 Li Q, Liu Y, Zhang HM, et al. Influence of DPYD genetic polymorphisms on 5-fluorouracil toxicities in patients with colorectal cancer: a meta-analysis. *Gastroenterol Res Pract* 2014; **2014:** 827989.