Opdam and colleagues agree with us that the IVS14+1G>A (DPYD*2A) polymorphism within DPYD, the gene encoding for dihydropyrimidine dehydrogenase, is strongly associated with severe, potentially lethal toxicity to standard dose fluoropyrimidines [i.e., 5-fluorouracil (5-FU) and capecitabine]. Given its Caucasian prevalence of approximately 1% to 1.5%, however, Opdam and colleagues suggest that upfront genotyping for DPYD*2A would not be cost-effective. On this point, we disagree. In 2007, we initiated a prospective, multicenter trial with the objective of determining the safety, pharmacokinetics, and cost-effectiveness of pharmacogenetic-guided dosing in DPYD*2A variant allele carriers treated with capecitabine or 5-FU (clinicaltrials.gov: NCT00838370). At this year’s American Society of Clinical Oncology proceeding, we presented our interim analysis based on the first 1,700 patients who were included in this trial (2). In brief, patients were prospectively screened for DPYD*2A before start of treatment with capecitabine or 5-FU. DPYD*2A variant allele carriers were treated with an initially reduced dose of 50% or more, followed by further dose titration based on clinical tolerance. Toxicity of treatment was compared with 45 historical DPYD*2A controls who were identified among 3,391 patients in 9 cohort studies who had been treated with full-dose fluoropyrimidine (1, 3–10). The cost-effectiveness analysis was carried out in parallel with the clinical trial from a health care payer perspective. Analysis was carried out using a probabilistic decision analytic model and included only direct medical costs. Genotyping costs were €75 ($102) per test.

Opdam and colleagues and van Kuilenburg and colleagues express their concerns about our haplotypes analysis. Specifically, they state that our haplotype analysis is a reliable data source, whereas the inaccuracy of haplotype estimation increases with low LD. However, the software inference increases with low LD. However, the software (Phase v2.1) does take locus spacing into account as well as the decay of LD over distance, and, in contrast to the concerns of van Kuilenburg and colleagues, it can additionally handle "nonblocklike" patterns of LD (11). Moreover, a study that compared the 5 leading software algorithms in haplotype inference showed that all software, Phase v2.1 provided the most accurate estimates (12). Finally, as the estimate accuracy of haplotype reconstruction increases with increasing sample size, we may state that our haplotype analysis is a reliable data source, given our large data set of 568 patients with almost no missing genotype data.

Of the total of 1,700 patients screened, 17 proved to be heterozygous polymorphic for DPYD*2A (1.0%). These DPYD*2A mutation carriers could be safely treated at a median fluoropyrimidine dose intensity per cycle of 48% (range, 24%–91%). The average risk of grade 3 or higher toxicity thereby reduced from 68% in historical controls to 15% by genotype-guided dosing; drug-induced death reduced from 10% to 0%. The pharmacokinetic analysis proved that the systemic exposure to 5-FU by adaptive dosing was comparable with the exposure in wild-type patients treated with full-dose therapy. The cost-effectiveness analysis showed that the average total health care costs per patient were slightly lower for screening (£5,839 or $7,929) than for nonscreening (£5,854 or $7,950).

This study is the largest cohort ever screened for DPYD*2A and is the first study that shows that patients with the variant genotype can be safely treated by adaptive dosing. Moreover, in contrast to the opinion by Opdam and colleagues, our study shows that upfront genotyping is cost-effective. We conclude therefore that upfront genotyping of DPYD*2A should be considered the new standard of care in patients treated with fluoropyrimidines.

van Kuilenburg and colleagues express their concerns about our haplotypes analysis. Specifically, they state that the linkage disequilibrium (LD) between some of the included polymorphisms were too low for a reliable haplotype estimation. Indeed, the inaccuracy of haplotype inference increases with low LD. However, the software that we used (Phase v2.1) does take locus spacing into account as well as the decay of LD over distance, and, in contrast to the concerns of van Kuilenburg and colleagues, it can additionally handle "nonblocklike" patterns of LD (11). Moreover, a study that compared the 5 leading software algorithms in haplotype inference showed that all software, Phase v2.1 provided the most accurate estimates (12). Finally, as the estimate accuracy of haplotype reconstruction increases with increasing sample size, we may state that our haplotype analysis is a reliable data source, given our large data set of 568 patients with almost no missing genotype data.

SNPs and Haplotypes in DPYD and Outcome of Capecitabine–Response

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