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CORRESPONDENCE

Reply to T. Magnes et al

We thank Magnes et al[1] for their letter in support of implementing prospective *DPYD* genotyping in patients treated with fluoropyrimidine-based chemotherapy. Our recently published study showed that upfront genotyping of *DPYD**2A followed by genotype-guided dose adjustment strongly decreased the incidence of severe adverse events, prevented lethal toxicity, and was cost saving in patients treated with fluoropyrimidines.[2]

This first, to our knowledge, prospective *DPYD* genotype-guided dosing study was based on hundreds of earlier laboratory and clinical studies that demonstrated the association of genetic variants in *DPYD* and fluoropyrimidine-induced severe toxicity. Nonetheless, international acceptance and implementation of *DPYD* genotyping as a routine standard-of-care procedure for every patient to be treated with fluoropyrimidine-based chemotherapy have proven to be challenging, as also noted by Magnes et al.[1] In fact, some guidelines even advise—for unknown reasons—against genotyping for dihydropyrimidine dehydrogenase (DPD) deficiency, despite acknowledgment of the increased risk.[3]

What hampers implementation of genotyping for DPD deficiency? It certainly is not lack of understanding of the mechanism, because there is a clear molecular basis for DPD deficiency (ie, *DPYD**2A encodes a truncated protein that has no residual enzyme activity).[4] Similar effects on protein function have been established for other *DPYD* mutations, such as *DPYD* c.2846A>T and c.1129-5923C>G, which both significantly reduce DPD enzyme activity.[5,6] Consequently, after administration of fluorouracil (FU) or capecitabine, genetically induced DPD deficiency results in increased and prolonged systemic FU exposure, coinciding with increased risk of severe, potentially lethal toxicity.[2] Moreover, a literature study showed that as many as 10% of the *DPYD**2A carriers who received the standard dose of FU or capecitabine deceased shortly after start of treatment as a result of drug-induced toxicity.[2] Finally, two systematic reviews and meta-analyses provide the highest level of evidence, both in favor of *DPYD* genotyping.[7,8]

Frequently mentioned arguments against genotyping include low polymorphism frequency of *DPYD**2A (1% to 2%) and consequently low sensitivity of the test (ie, not all DPD-deficient patients are herewith identified). However, our study showed that screening is a life- and cost-saving strategy; therefore, low polymorphism frequency may not be a good argument for not screening patients. In this regard, Magnes et al[1] raise the right question: Would the test be questioned if FU were a new drug?

Supported by several examples, Magnes et al[1] state that for various (newer) drugs, diagnostic tests are routinely performed before administration, and this has not given rise to any form of discussion. Moreover, marketing authorization agencies today specifically stimulate the development of genomic biomarkers to maximize patient benefit.[9] Given this development, there would certainly be less discussion about implementing *DPYD* pharmacogenetics if FU were a new drug.

Thus, given the current situation—an old drug with a new biomarker test—and given the fact that prospective evidence of genotype-guided dosing has now been provided, we emphasize the need for incorporation of *DPYD* genotyping into every relevant clinical pathway and treatment guideline. Furthermore, the summaries of product characteristics for FU and capecitabine state a known DPD deficiency as a contraindication. Importantly, our study showed that a (partial) DPD deficiency is not necessarily a contraindication for fluoropyrimidine-based chemotherapy; DPD-deficient patients can be treated safely using genotype-guided dosing. In this way, important anticancer drugs such as FU and capecitabine, forming the cornerstone of treatment for GI malignancies, do not have to be withheld.

Upfront *DPYD* genotyping as a standard screening procedure was shown to be feasible and did not delay start of treatment. Because genotyping techniques are readily available in most hospitals, clinicians should have easy access to this life-saving screening strategy. Furthermore, at the current genotyping cost of €75 (US$82), Magnes et al[1] calculated that the cost per life-year gained by *DPYD**2A genotyping would be €7,500 (US$8,175) and €30,000 (US$32,700) in the adjuvant and palliative treatment of colon cancer, respectively. Bearing in mind that genotyping costs are continuing to decrease, prospective *DPYD* genotyping remains far below the general cost-effectiveness threshold as used by the National Institute for Health and Clinical Excellence and other globally set thresholds.[10]

Our first prospective *DPYD* genotyping study was based on screening for only *DPYD**2A.[2] In our current national study (ClinicalTrials.gov identifier NCT02324452), the genotyping package consists of four *DPYD* single-nucleotide polymorphisms (ie, *DPYD**2A, c.2846A>T, c.1236G>A/HapB3, and c.1679T>G), for which 50%, 25%, 25%, and 50% reduced starting doses in heterozygous carriers are administered, respectively. By expanding the test with these additional polymorphisms, we aim to increase the sensitivity of the test to further prevent severe and lethal drug-induced toxicity.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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