Pharmacogenetic testing to predict serious toxicity from 5-Fluorouracil (5-FU) for patients administered 5-FU-based chemotherapy for cancer

BlueCross BlueShield Association

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Authors’ conclusions
It has been tempting to postulate alterations in activity of key enzymes such as DPD and TS in the 5-FU metabolic pathway as the causal basis for 5-FU toxicity, and specific genetic variants of the genes coding for those enzymes as the starting points in the causal chain. Indeed, patients who are homozygous (i.e., have the same variant sequence in both gene copies) for DPD-inactivating mutations in the DPD gene uniformly experience early, severe, and potentially fatal toxicity reactions when administered standard 5-FU doses. However, homozygosity or compound heterozygosity (more than 1 variant sequence, distributed across both gene copies) for DPD-inactivating mutations was rarely reported in the studies included in this Assessment and heterozygous DPYD variants were observed in relatively small proportions of patients with grade 3 to 4 toxicity. Moreover, not all patients with DPYD variants experience toxicity (even when variants assessed are limited to those with prior associations with toxicity). The clinical validity evidence for each of the 3 types of TS gene variants is similarly poor in terms of the ability of TYMS variants to predict which patients are likely to experience severe 5-FU toxicity. In summary, testing for genetic variants of the genes coding for DPD and TS enzymes has poor predictive value for 5-FU toxicity and no studies have shown that it is useful in directing 5-FU dose reductions to lower toxicity without adversely affecting tumor response.

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