CLINICAL UPDATE

Testing for 5-FU Toxicity

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TheraGuide 5—FU™

TheraGuide 5-FU™ is the first and only comprehensive test for predisposition for 5-FU toxicity caused by variations in the *DPYD* and *TYMS* genes. It employs full sequencing of the *DPYD* gene and analysis of the *TYMS* gene.

1 in 4 individuals

carry variations in either the *DPYD* or *TYMS* genes that will increase their risk of dose-limiting toxicty.

TheraGuide 5-FU™

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Clinical Support, Healthcare Information and Myriad Reimbursement Assistance Program (MRAP): 1-800-4-MYRIAD

Testing for 5-FU Toxicity: *DPYD* (DPD) and *TYMS* (TS)

How common is 5-FU toxicity?

As many as 1 in 3 patients receiving 5-FU related therapy experience dose limiting, and sometimes life-threatening, toxicity that is largely avoidable. By predicting 5-FU or capecitabine toxicity, oncologists can provide enhanced therapeutic choices for improved patient outcomes (either by dose reduction or choice of alternative therapy)

What is the role of *DPYD* in 5-FU toxicity?

Dihydropyrimidine dehydrogenase deficiency (DPD) is a pharmacogenetic condition that results in toxicity when patients are exposed to 5-FU. This condition is due to variations in the *DPYD* gene, which encodes the DPD enzyme. Approximately 80-85% of therapeutically administered 5-FU is normally degraded through interaction with DPD, with the remaining 15% of active drug available as a cytotoxin. In the absence of typical DPD activity, the expected amount of 5-FU is not degraded, potentially leading to significant patient toxicity.

What is the role of *TYMS* in 5-FU toxicity?

Other genetic abnormalities have also been associated with 5-FU toxicity. Reduction in the activity of the 5-FU therapeutic target thymidylate sythetase (TS) produced toxic effects that are clinically indistinguishable from that which is associated with DPD deficiency. Genetic variations in *TYMS*, particularly in the promoter region, have been associated with reduced TS production and subsequent 5-FU toxicity.

What is the toxicity risk for patients with *DPYD* or *TYMS* variants?

Variations in the *DPYD* and *TYMS* genes are associated with up to a 60% risk of severe to life-threatening toxicity to 5-FU or capecitabine.

How common are *DPYD* and *TYMS* variants?

Up to 25% (1/4) of patients will have variations in the *DPYD* and *TYMS* genes that are associated with elevated risk of dose limiting toxicity to 5-FU.

What is TheraGuide 5-FU™?

TheraGuide 5-FU™ is the first and only comprehensive test for predisposition for 5-FU toxicity caused by variations in the *DPYD* and *TYMS* genes. It employs the full sequencing of the *DPYD* gene and analysis of the *TYMS* gene.

How do patients benefit from TheraGuide 5-FU™?

By predicting 5-FU or capecitabine toxicity, oncologists can provide enhanced therapeutic choices for improved patient outcomes (either by dose reduction or choice of alternative therapy).

Bottom Line: *DPYD* full sequence analysis and *TYMS* variant analysis with TheraGuide 5-FU™ will allow the clinician to identify and monitor 5-FU therapeutic benefits on an individual level.

1. Morel, A. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-flurorouracil tolerance. *Mol Cancer Ther* 2006. 5(11):289-291.
2. Pullarkat, S. T., J. Stoehlmacher, et al. Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. *Pharmacogenomics J* 2001.1(1): 65-70.
3. Lecomte T, Ferraz JM, Zinzindohoue F, et al. Thymidylate synthase gene polymorphism predicts toxicity in colorectal cancer patients receiving 5-fluorouracil-based chemotherapy. *Clin Cancer Res.* 2004 Sep 1;10(17):5880-8.
4. Ichikawa W, Takahashi T, Suto K, et al. Orotate phosphoribosyltransferase gene polymorphism predicts toxicity in patients treated with bolus 5-fluorouracil regimen. *Clin Cancer Res.* 2006 Jul 1;12(13):3928-34.

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