



## Indications for Ordering

- Pre-therapeutic identification of individuals who should avoid or may require unconventional doses of 5-FU.
- Screening of individuals with a personal or family history of adverse drug reactions, including therapeutic failure, when treated with 5-FU.

## Interpretation

- Genotype should be interpreted with clinical information; consultation with a clinical pharmacist is recommended.
- Negative: no mutations were detected.
  - This genotype does not predict 5-FU sensitivity or an increased risk for 5-FU related toxicity.
- Positive:
  - The detection of a *DPYD* or *TYMS* mutation predicts an increased sensitivity to 5-FU and may lead to increased risk for toxicity. Alternative chemotherapeutic agents, therapeutic drug monitoring, altered 5-FU doses, or increased surveillance for adverse drug reactions may be indicated.
  - The detection of an *MTHFR* mutation is associated with decreased MTHFR activity and increased rate of TS reactivity, but the impact of this variant on 5-FU efficacy and toxicity is not clear.

## Methodology

- Multiplex PCR and detection primer extension to detect the following eight gene mutations associated with an increased risk for 5-FU toxicity and/or altered response:

Gene	Variant	Variant Common Name	Predicted Consequence
<i>DPYD</i>	IVS14+1G>A	*2	Abolished DPD activity
	c.85T>C	*9A	Reduced DPD activity
	c.1679T>G	*13	Reduced DPD activity
	c.-1590T>C		Reduced DPD activity
	c.2846A>T		Reduced DPD activity
<i>TYMS</i>	rs16430	1494 del TTAAAG	Reduced TS expression
<i>MTHFR</i>	c.677C>T	C667T	Reduced MTHFR activity
	c.1298A>C	A1298C	Reduced MTHFR activity

- Clinical sensitivity and specificity are unknown.
- Analytical sensitivity and specificity for the mutations detected are 99 percent.

## Limitations

- Only the targeted *DPYD*, *MTHFR*, and *TYMS* mutations will be detected.
- Mutations in other genes and non-genetic factors that may affect drug metabolism are not identified.
- Rare diagnostic errors can occur due to primer-site mutations.

## References

1. Lecomte T, et al. Thymidylate synthase gene polymorphism predicts toxicity in colorectal cancer patients receiving 5-fluorouracil-based chemotherapy. *Clin Cancer Res* 2004;10:5880–8.
2. Schwab M, et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the german 5-FU toxicity study group. *J Clin Oncol* 2008;26(13):2131–8.
3. Sohn K, et al. Effect of the methylenetetrahydrofolate reductase C677T polymorphism on chemosensitivity of colon and breast cancer cells to 5-fluorouracil and methotrexate. *J Natl Cancer Inst* 2004;96:134–44.
4. Zhag H, et al. *DPYD*\*5 gene mutation contributes to the reduced *DPYD* enzyme activity and chemotherapeutic toxicity of 5-FU. *Med Oncol* 2007;24:251–8.

## Test Information

2002420

5-Fluorouracil Sensitivity (*DPYD*, *TYMS* and *MTHFR*) 8 Mutations

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).