



Molecular Diagnostic Laboratory
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Thymidylate Synthase Enhancer Region (TYMS)

Tandem repeats on the *TYMS* gene indicative of response to 5-fluorouracil (5-FU), a chemotherapeutic agent

Indications for Molecular Testing

- Patients diagnosed with colorectal or gastric cancer who are candidates for 5-fluorouracil chemotherapy (5-FU)

Testing Methodology

A single polymerase chain reaction (PCR) is used to detect a tandemly repeated sequence variation in the 5' untranslated region of the *TYMS* gene. The number of repeats observed is polymorphic, with the most common alleles containing 2 or 3 copies of the 28 bp repeat. These genotypes also correlate with increased *TYMS* gene expression and variation in the effectiveness of the chemotherapeutic responses to 5-FU therapy.

(PCR is utilized pursuant to a license agreement with Roche Molecular Systems, Inc.)

Interpretation of DNA analysis

5-FU is a first line chemotherapeutic regimen for colorectal cancer, both in cases of metastatic and adjuvant cancer. Thymidylate synthase (TS) is a target enzyme of the cancer chemotherapeutic agent 5-fluorouracil (5-FU).

The active metabolite of 5-FU binds to the *TYMS* protein and forms a stable, inactive complex. Several genotypes are possible when looking at the VNTR in the 5' untranslated region of the human *TYMS* gene. The most common are double and triple tandem repeats; people of Kenyan, Ghanaian, African American, and British Caucasian descent may have other rare alleles with four and nine repeats. The homozygous occurrence of the 2-copy repeat and the heterozygous 2/3 variation have been associated with a 3-fold increased probability for colorectal tumor downstaging following 5-FU treatment, relative to homozygous 3-copy repeat carriers. The 2/2 genotype occurs in about 20% of Caucasian patients, 2/3 in about 50%, and the 3/3 genotype occurs in about 30%. The 3-copy repeat allele produces greater *TYMS* gene expression and higher *TYMS* activity, thus resulting in poorer response to 5-FU. Clinical studies suggest that Stage III colorectal cancer patients that are homozygous for the 3-copy allele do not benefit from neoadjuvant 5-FU therapy. Knowledge of the TS genotype could help to predict response to 5-FU chemotherapy and survival in colorectal cancer.

Specimen Requirements

Peripheral Blood--1 lavender-top (EDTA) tube. Invert several times to mix blood. Do not freeze, forward promptly at ambient temperature to the following address:

Molecular Diagnostic Laboratory
Barnes-Jewish Hospital North, Room 2445
Mail Stop 90-28-372
216 South Kingshighway
St. Louis, MO 63110

Clinical information must be provided with specimen referral in order to correctly interpret test results.

Current Pricing

Contact Lab Customer Service for current pricing 314 362-1470.

CPT codes: 83907, 83890, 83898, 83894, 83912.

Peters GJ, Backus HHJ, Freemantle S, van Triest B, Codacci-Pisanelli G, van der Wilt CL, et al. Induction of thymidylate synthase as a 5-fluorouracil resistance mechanism. *Biochimica et Biophysica Acta* 2002; 1587:194-205

Pullarkat ST, Stoehimacher J, Ghaderi V, Xiong Y-P, Ingles SA, Sherrod A, et al., Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. *The Pharmacogenomics Journal* 12 March 2001;1: 65-70.