Overview

Useful For
Identifying individuals at increased risk of toxicity when considering 5-fluorouracil (5-FU) and capecitabine chemotherapy treatment

For an individual with suspected dihydropyrimidine dehydrogenase (DPD) deficiency, this test may be useful in identifying variants associated with decreased or absent DPD enzyme activity

Genetics Test Information
This is a pharmacogenomics test associated with 5-fluorouracil and capecitabine drug sensitivity. Biallelic variation in the \textit{DPYD} gene is also associated with dihydropyrimidine dehydrogenase (DPD) deficiency.\(^1\) Individuals who have variations identified in the \textit{DPYD} may benefit from genetic consultation.

Special Instructions
- Informed Consent for Genetic Testing
- Multiple Whole Blood EDTA Genotype Tests
- Pharmacogenomic Associations Tables
- Informed Consent for Genetic Testing (Spanish)

Method Name
Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available
Yes

Specimen

Specimen Type
Varies

Specimen Required
Multiple whole blood EDTA genotype tests can be performed on a single specimen after a single extraction. See Multiple Whole Blood EDTA Genotype Tests in Special Instructions for a list of tests that can be ordered together.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.
**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Supplies:** DNA Saliva Collection Kit (T651)

**Specimen Type:** Saliva

**Container/Tube:** Oragene DNA Self-Collection Kit (T651: fees apply)

**Specimen Volume:** Full tube

**Collection Instructions:**

1. Fill tube to line.

2. Send specimen in original container per kit instructions.

**Specimen Stability Information:** Ambient

**Specimen Type:** DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/Refrigerated

**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - *Informed Consent for Genetic Testing* (T576)
   - *Informed Consent for Genetic Testing (Spanish)* (T826)

2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
   - *Pharmacogenomics Test Request* (T797)
   - *Therapeutics Test Request* (T831)

**Specimen Minimum Volume**

Blood: 0.45 mL
Saliva: Full tube of saliva
Test Definition: DPYDG
DPYD Full Gene Sequencing

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>Varies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical and Interpretive

Clinical Information

5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors.

The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation (table 1). This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity. (2,3) Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment. (4) In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation.

Table 1. Known Genetic Variations Associated with Fluoropyrimidine Treatment

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA numbering</th>
<th>Alternative Name</th>
<th>Enzyme Activity</th>
<th>Phenotypeâ€”#128;�?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPYD</td>
<td>No variations identified</td>
<td>*1</td>
<td>No activity or significantly reduced activity</td>
<td>High risk for fluoropyrimidine toxicity</td>
</tr>
<tr>
<td></td>
<td>c.1905+1G-&gt;A</td>
<td>*2A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1679T-&gt;G</td>
<td>*13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1898delC</td>
<td>*3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.299_302delTCAT</td>
<td>*7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1156G-&gt;T</td>
<td>*12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.2846A-&gt;T</td>
<td>rs67376798</td>
<td>Reduced activity</td>
<td>Increased risk for fluoropyrimidine toxicity</td>
</tr>
<tr>
<td></td>
<td>c.1129-5923C-&gt;G</td>
<td>rs75017182</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.703C-&gt;T</td>
<td>*8</td>
<td>Probable reduced function</td>
<td>Increased risk for fluoropyrimidine toxicity</td>
</tr>
<tr>
<td></td>
<td>c.2983G-&gt;T</td>
<td>*10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1003G-&gt;T</td>
<td>*11</td>
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Test Definition: DPYDG
DPYD Full Gene Sequencing

<table>
<thead>
<tr>
<th>c.557A-&gt;G</th>
<th>rs115232898</th>
<th>Normal activity**</th>
<th>Normal risk for fluoropyrimidine toxicity</th>
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<tbody>
<tr>
<td>c.1601C-&gt;T</td>
<td>*4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.1627A-&gt;G</td>
<td>*5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2194C-&gt;T</td>
<td>*6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.85T-&gt;C</td>
<td>*9A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Other or novel variations, besides those listed here, may also impact fluoropyrimidine-related side effects and tumor response and will be reported if detected.

**Alleles that are categorized as having normal enzyme activity (e.g., *4, *5, *6, *9A) will not be reported if detected because variants with normal enzyme activity are not expected to impact fluoropyrimidine-related side effects and tumor response.

The DPYD gene is located on chromosome 1 and contains 2 transcripts. The longer transcript (NM_000110.3) contains 23 exons, and the shorter transcript (NM_001160301.1) contains 6 exons, with exon 6 being unique to this transcript. All exons from the longer transcript (NM_000110.3) and exon-intron boundaries are assessed.

Genetic variations involved in the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes including toxicity and tumor response.

Reference Values
An interpretive report will be provided.

Interpretation
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions
Samples may contain donor DNA if obtained from patients who received heterologous blood transfusions or allogeneic blood or marrow transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic blood or marrow transplantation, a pretransplant DNA specimen is recommended for testing.

Dihydropyrimidine dehydrogenase (DPYD) genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's DPYD status.

Rare genetic variants exist that could lead to false-negative or false-positive results. Other variants in the primer binding regions can affect the testing, and ultimately, the genotype assessment made.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Large deletions or rearrangements are not detected by this assay, and these may affect DPYD protein expression and their impact on fluoropyrimidine related side effects and tumor response.
Sometimes a genetic alteration of unknown significance may be identified. In this case, testing of appropriate family members may be useful to determine pathogenicity of the alteration.

This test is not designed to provide specific dosing or drug selection recommendations and is to be used as an aid to clinical decision making only. Drug-label guidance should be used when dosing patients with medications regardless of the predicted phenotype.

**Clinical Reference**
4. FDA Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

**Performance**

**Method Description**
Genomic DNA is extracted from whole blood. The dihydropyrimidine dehydrogenase (DPYD) gene is amplified by PCR. The PCR products are then purified and sequenced in both directions using fluorescent dye-terminator chemistry. Sequencing products are separated on an automated sequencer and trace files analyzed for variations in the exons and intron/exon boundaries of all 23 exons of the DPYD gene (using gene transcript NM_000110.3) using mutation detection software and visual inspection.(Unpublished Mayo method)

**PDF Report**
No

**Day(s) and Time(s) Test Performed**
Varies; 8 a.m.

**Analytic Time**
5 days (Not reported on Saturday or Sunday)

**Maximum Laboratory Time**
10 days

**Specimen Retention Time**
Whole blood/Saliva: 2 weeks; Extracted DNA: 2 months
Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81232

LOINC® Information

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