Medical Policy

Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

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Policy Number: 318
BCBSA Reference Number: 2.04.68

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

My5-FU™ testing or other types of assays for determining 5-fluorouracil area under the curve in order to adjust 5-FU dose for colorectal cancer patients or other cancer patients is INVESTIGATIONAL.

TheraGuide® testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is INVESTIGATIONAL.

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
<th>Inpatient</th>
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<tbody>
<tr>
<td></td>
<td>This is not a covered service.</td>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes
There is no specific CPT code for this service.

HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>S3722</td>
<td>Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil</td>
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ICD-9 Diagnosis Codes
Investigational for all diagnoses.

Description
Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. Two approaches have been proposed for modifying use of 5-FU:
1. Dosing of 5-FU in cancer patients to a predetermined area under the curve (AUC) serum concentration target: Accurate AUC determination relies on sampling at pharmacokinetically appropriate times, as well as on accurate methods of 5-FU serum concentration measurement. Available measurement methods are complex, making them less amenable to routine clinical laboratory settings.
2. Genetic testing for mutations affecting 5-FU metabolism: Genetic mutations may affect activity of enzymes involved in 5-FU metabolism. Currently-available polymerase chain reaction (PCR) tests assess specific mutations in genes encoding dihydropyrimidine reductase (DPYD) and thymidylate synthase (TYMS), enzymes in the catabolic and anabolic pathways of 5-FU metabolism, respectively.

Background
5-FU is a widely used antineoplastic chemotherapy drug that targets TYMS, an enzyme involved in DNA production. 5-FU has a narrow therapeutic index; doses recommended for effectiveness often are limited by hematologic and gastrointestinal toxicity. Moreover, patients administered the same fixed-dose, continuous-infusion regimen of 5-FU have wide intra- and interpatient variability in systemic drug exposure, as measured by plasma concentration or, more accurately, by AUC techniques. AUC is a measure of systemic drug exposure in an individual over a defined period of time.

In general, the incidence of grade 3 to 4 toxicity (mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Several studies also have reported statistically significant positive associations between 5-FU exposure and tumor response. In current practice, however, 5-FU dose is reduced when symptoms of severe toxicity appear, but is seldom increased to promote efficacy.

Based on known 5-FU pharmacology, it is possible to determine a sampling scheme for AUC determination and to optimize an AUC target and dose adjustment algorithm for a particular 5-FU chemotherapy regimen and patient population. For each AUC value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target AUC without overshooting and causing severe toxicity.

In clinical research studies, 5-FU blood plasma levels most recently have been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass spectrometry.
Both methods require expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings. One commercially available alternative is Saladax Biomedical's My5-FU™, an immunoassay designed to measure patients' exposure to 5-FU to help oncologists adjust and optimize 5-FU dosing. My5-FU™ was originally marketed in the U.S. by Myriad Genetics as OnDose® under patents licensed from Saladax Biomedical (Bethlehem, PA). (1) In June 2013, rights to the assay reverted to Saladax Biomedical. (2)

**Metabolism of 5-Fluorouracil**

5-FU is a pyrimidine antagonist, similar in structure to the normal pyrimidine building blocks of RNA (uracil) and DNA (thymine). More than 80% of administered 5-FU is inactivated and eliminated via the catabolic pathway; the remainder is metabolized via the anabolic pathway.

- Catabolism of 5-FU is controlled by the activity of **DPYD**. Because **DPYD** is a saturable enzyme, the pharmacokinetics of 5-FU are strongly influenced by the dose and schedule of administration. (3) For example, 5-FU clearance is faster with continuous infusion compared with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic mutations in **DPYD**, located on chromosome 1, can lead to reduced 5-FU catabolism and increased toxicity. Many variants have been identified (eg, IVS14+1G>A [also known as **DPYD*2A**], 2846A>T [D949V]). **DPYD** deficiency is an autosomal codominantly inherited trait. (4)

- The anabolic pathway metabolizes 5-FU to an active form that inhibits DNA and RNA synthesis by competitive inhibition of **TYMS** or by incorporation of cytotoxic metabolites into nascent DNA. (5) Genetic mutations in **TYMS** can cause tandem repeats in the **TYMS** enhancer region (TSER). One variant leads to 3 tandem repeats (**TSER*3**) and has been associated with 5-FU resistance due to increased tumor **TYMS** expression in comparison with the **TSER*2** variant (2 tandem repeats) and wild-type forms.

- Myriad Genetics has developed a PCR test, TheraGuide®, to assess certain mutations in **DPYD** and **TYMS**. The Myriad Genetics website estimates that “up to 25% of individuals have variations in the **DPYD** and/or **TYMS** genes that are associated with an increased risk of toxicity to 5-FU.” (6) ARUP Laboratories also offers **DPYD** and **TYMS** mutation testing. (5)

**Summary**

Prior evidence supports the wide variability of 5-fluorouracil (5-FU) plasma levels when patients are placed on a fixed-dose regimen; high exposure is associated with toxicity, but higher exposure up to the limits of toxicity is also associated with better tumor response to treatment. Area under the curve (AUC) laboratory testing methods to better measure 5-FU exposure during treatment of cancer and validated algorithms to modify subsequent dosing may improve response and reduce toxicity. However, currently available evidence is limited and insufficient to draw conclusions about the impact of 5-FU exposure measurement and AUC-targeted dose adjustment on outcomes of patients administered contemporary chemotherapy regimens for colorectal or head and neck cancer. Given the lack of relevant studies, a similar conclusion is reached for use of 5-FU in other cancers.

Impaired function of enzymes in 5-FU metabolic pathways may contribute to toxicity and/or reduced efficacy. However, current evidence for pretreatment testing for genetic mutations in dihydopyrimidine dehydrogenase (**DPYD**) and/or thymidylate synthase (**TYMS**) comprises associational studies only. Impacts on treatment selection and 5-FU dosing have not been demonstrated. Evidence for improved outcomes in patients eligible for 5-FU chemotherapy is lacking.

**Policy History**

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<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


32. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer. TEC Assessments 2010; volume 24, tab 13.


