MEDICAL POLICY – 2.04.68
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

BCBSA Ref. Policy: 2.04.68
Effective Date: June 1, 2017
Last Revised: May 2, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
N/A

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Fluorouracil (5FU) is a chemotherapy used to treat different cancers. These are colon, rectum, breast, stomach, and pancreatic cancer. As with all chemotherapies, the goal is to give enough medication to treat the cancer without causing ongoing harm to the rest of the body. Blood tests have been developed that try to give information about how much 5FU to use during each treatment. These tests are investigational. This means they are not proven. There is not enough published medical evidence to show that these blood tests lead to better results. Similarly, genetic tests have been created that try to show how the body processes (metabolizes) 5FU. These genetic tests are investigational. There is not enough medical evidence to show if these tests provide enough useful information to affect overall health.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
<table>
<thead>
<tr>
<th>Test</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>My5-FU™</td>
<td>My5-FU™ testing or other types of assays for determining the appropriate dose of 5-fluorouracil to treat certain cancer patients is considered investigational</td>
</tr>
<tr>
<td></td>
<td>Note: My5-FU™ was previously known as OnDose® (Myriad Genetics under license from Saladax Biomedical); and the TheraGuide® test is no longer commercially available.</td>
</tr>
<tr>
<td>DPYD or TYMS genes</td>
<td>Testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) genes to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.</td>
</tr>
</tbody>
</table>

**Coding**

**CPT**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis) that includes the following test:</td>
</tr>
<tr>
<td></td>
<td>• DPYD (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), IVS14+1G&gt;A variant</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) that includes the following test:</td>
</tr>
<tr>
<td></td>
<td>• TYMS (thymidylate synthetase) (e.g., 5-fluorouracil/5-FU drug metabolism), tandem repeat variant</td>
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<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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</table>

**HCPCS**

<table>
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<th>Code</th>
<th>Description</th>
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<tr>
<td>S3722</td>
<td>Dose optimization by area-under-the-curve (AUC) analysis for infusional 5-fluorouracil (5-FU) that is specific for the My5-FU test.</td>
</tr>
</tbody>
</table>

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Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

Description

Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-FU: (1) dosing based on determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-FU metabolism. For genetic testing, currently available polymerase chain reaction tests assess specific variants in genes encoding dihydropyrimidine reductase (DPYD) and thymidylate synthase (TYMS) in the catabolic and anabolic pathways of 5-FU metabolism, respectively.

Background

5-fluorouracil

The agent 5-fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (TYMS) enzyme, which is involved in DNA production. 5-FU has been used
for many years to treat solid tumors (eg, colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 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 area under the curve (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.

**Measuring Exposure to 5-FU**

**Laboratory Testing**

Patient exposure to 5-FU is most accurately described by estimating the AUC, the total drug exposure over a defined period of time. 5-FU exposure is influenced by method of administration, circadian variation, liver function, and the presence of inherited dihydropyrimidine reductase (DPYD)-inactivating genetic variants that can greatly reduce or abolish 5-FU catabolism. As a result, both inter- and intrapatient variability in 5-FU plasma concentration during administration is high.

Determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the United States, Saladax Biomedical offers a commercial immunoassay (My5-FU) that quantifies plasma 5-FU concentration from a blood sample drawn during continuous infusion at steady state (18-44 hours after the start of infusion) and provides a dose-adjustment algorithm to maintain plasma 5-FU AUC between 20 and 30 mg/h/L during the next cycle.¹
Genetic Testing

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. For example, 5-FU clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic variants 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.

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. Genetic variants 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 compared with the TSER*2 variant (2 tandem repeats) and wild-type forms.

Summary of Evidence

For individuals who have cancer for whom treatment with 5-fluorouracil (5-FU) is indicated who receive laboratory assays to determine 5-fluorouracil area under the curve (that is, the most appropriate dosage), the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity and treatment-related morbidity. A systematic review of observational studies on analytic validity studies found good correlation between test results; however, reviewers concluded that selected studies had a high risk of bias due to excluded samples. Several analyses of patients with colorectal cancer have evaluated clinical validity. For example, 1 study found that the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring versus body surface area (BSA) monitoring, but progression-free survival did not differ between groups in patients with stage IV or recurrent cancer. No RCTs or nonrandomized comparative studies were identified comparing health outcomes in cancer patients who did and did not have 5-FU dose adjustment using the My5-FU assay and who were treated with chemotherapy regimens used in current clinical practice. A
systematic review of the available literature found a significantly higher response rate with BSA-based monitoring and no significant difference in toxicity. Most data were from observational studies and the RCTs were conducted in the 1980s when different chemotherapy protocols were used. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer for whom treatment with 5-FU is indicated who receive genetic testing for variants (eg, in DPYD and TYMS) affecting 5-FU metabolism, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A 2010 TEC Assessment concluded that DPYD and TYMS variant testing had poor prognostic capacity to identify patients likely to experience severe 5-FU toxicity. Since publication of that Assessment, no prospective trials comparing efficacy and toxicity outcomes in patients who did and did not undergo pretreatment DPYD and/or TYMS testing have been published. One study compared outcomes in patients undergoing pretreatment DPYD testing with historical controls who did not receive testing. In that study, rates of grade 3 or higher toxicity were lower in patients who had genetic testing; however, the study was not randomized and lacked concurrent controls. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials Clinical Input Received From Physician Specialty**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<td></td>
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<tr>
<td><strong>AUC-guided dosing of 5-FU</strong></td>
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<tr>
<td>NCT02055560³</td>
<td>Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-FU Exposure Optimization Testing</td>
<td>350</td>
<td>Dec 2016</td>
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<tr>
<td>NCT00943137</td>
<td>The Optimisation of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer</td>
<td>55</td>
<td>Jun 2017</td>
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</table>
### Practice Guidelines and Position Statements

**National Comprehensive Cancer Network (NCCN)**

Although current National Comprehensive Cancer Network (NCCN) guidelines acknowledge that the “selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex,” NCCN does not recommend using the area under the curve as guidance for 5-fluorouracil (5-FU) dosing or genetic testing for DPYD and/or TYMS variants in patients with colon, rectal, breast, gastric, pancreatic cancer, or head and neck cancers.

**Clinical Pharmacogenetics Implementation Consortium (CPIC)**

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in 2009 as a shared project between PharmGKB, an internet research tool developed by Stanford University, and the Pharmacogenomics Research Network of the National Institutes of Health. In 2013, CPIC published an evidence-based guideline for DPYD genotype and fluoropyrimidine dosing. The guideline did not address testing.

**National Institute for Health and Care Excellence (NICE)**

In 2014, the National Institute of Health and Care Excellence published evidence-based diagnostics guidance on the 5-FU assay for 5-FU chemotherapy dose adjustment. The guidance stated: “The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU..."
assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice.”

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

- **My5-FU™** (Saladax Biomedical) is available under the auspices of CLIA. Other clinical laboratories may offer in-house assays to measure 5-fluorouracil (5-FU) area under the curve.

- **TheraGuide®** (Myriad Genetics) was a laboratory-developed test but has been discontinued. Other laboratories may offer in-house assays for DPYD and TYMS mutation testing and ARUP Laboratories offers a test that is equivalent to TheraGuide (5-FU toxicity and chemotherapeutic response, 7 mutations test).

References


27. 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;24:Tab 13.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>01/25/12</td>
<td>HCPCS code S3722 added.</td>
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<tr>
<td>05/22/12</td>
<td>Replace policy. Policy updated with literature search. References 20-22 added. No change to policy statement.</td>
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<tr>
<td>09/18/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<tr>
<td>05/28/13</td>
<td>Replace policy. Rationale section updated based on a literature review through February 2013. References 18 and 21 added; others renumbered or removed. Policy statement unchanged.</td>
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<tr>
<td>05/12/14</td>
<td>Annual Review. Title changed to include genetic testing. First investigational policy statement test name OnDose® changed to new test name MyS-FU™. New investigational policy statement for TheraGuide® testing for genetic mutations in DPYD or TYMS added. Policy updated with literature review through February 17, 2014. References 2, 4-7, 12, 15-16, 30-44 added; references 8, 17, 29 updated. Policy statements changed as noted. ICD-10 codes removed to support ICD-10 mapping project.</td>
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<td>06/01/16</td>
<td>Annual Review, approved May 10, 2016. Policy updated with literature review through February 2, 2016; references 27, 29, and 45 added. “TheraGuide” removed from policy statement since this test is no longer commercially available. Policy statements otherwise unchanged.</td>
</tr>
</tbody>
</table>

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U.S. Department of Health and Human Services
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