Description of Procedure or Service

5-Fluorouracil

The agent 5-Fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets TYMS, an enzyme 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 to 4 toxicity (mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Several studies have also 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 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 have most recently been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass spectrometry. Both methods require the 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.

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

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 (e.g., 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.

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). My5-FU™ (Saladax Biomedical) and genetic testing for variants in DPYD and TYMS for predicting risk of 5-fluourouracil toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of CLIA. (The LDT TheraGuide® by Myriad Genetics has been discontinued). 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 laboratory or genetic tests for use of 5-FU.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

My5-FU™ testing or other types of assays for determining 5-fluourouracil area under curve in order to adjust 5-FU dose is considered investigational for all applications.

Testing for genetic variants in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational for all applications.

BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Laboratory and Genetic Testing for Use of 5-Fluorouracil is covered
Not applicable.
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

When Laboratory and Genetic Testing for Use of 5-Fluorouracil is not covered

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 considered investigational.

Testing for genetic variants in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.

Policy Guidelines

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-fluorouracil area under the curve, 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. 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81232, 81346, S3722

CPT code 81400 includes the following test:
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

*DPYD* (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism),
*IVS14+1G>A* variant

* CPT code 81401 includes the following test:
  *TYMS* (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), tandem repeat variant

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**

- Medical Director – 4/2011
- Senior Medical Director – 4/2014
- Specialty Matched Consultant Advisory Panel 8/2017
- Specialty Matched Consultant Advisory Panel 8/2018

**Policy Implementation/Update Information**

5/10/11 New policy implemented. “OnDose™ 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 considered investigational.” Medical Director review 5/29/2011. Notification given 5/10/2011. Policy effective date, 8/16/11. (btw)
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/2011. No change to policy. (btw)

1/1/12 Added new 2012 HCPCS code, S3722, to the “Billing/Coding” section. (btw)

5/1/12 Reference added. (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy. (btw)

5/14/13 Reference added. (btw)

9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)

4/29/14 Policy title changed from “Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Patients Administered 5-FU for Cancer” to “Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer”. Description section updated to change the name of OnDose® to My5-FU® and to add information regarding TheraGuide®. Additional non-coverage statement added to policy indicating; “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 considered investigational.” Added the following statement to the When Not Covered section to indicate; “There is no specific CPT coding for the TheraGuide testing. The following codes may be used: 81400 and 81401. Policy Guidelines updated. Reference added. Senior Medical Director review 4/9/2014. Notification given 4/29/2014. Policy effective 7/1/2014. (btw)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

4/28/15 Reference added. (lpr)

10/1/15 Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)

4/29/16 Updated Description, Regulatory Status, and Policy Guidelines sections. Removed TheraGuide® from policy statement and Regulatory status section as this test is no longer commercially available. No change to policy intent. Reference added. (lpr)

9/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)

4/28/17 Updated Description and Policy Guidelines sections. Under “When Covered” changed “mutations” to “variants.” Reference added. No change to policy statement. (lpr)

9/15/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)

12/29/17 Added CPT codes 81232 and 81346 to Billing/Coding section. (lpr)

4/13/18 Reference added. (lpr)
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

9/28/18  Specialty Matched Consultant Advisory Panel review 8/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.