BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-134-0001
EFFECTIVE DATE June 1, 2014	**SUBJECT:** Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

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.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins.

BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

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 Saladex 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 Saladex 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)

MEDICAL POLICY STATEMENT:

BCNEPA will not provide coverage for the following as they are considered investigational:

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, or

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.

GUIDELINES:

Currently, U.S. Food and Drug Administration (FDA)-approved tests for 5-FU AUC measurement and for *DPYD*/*TYMS* mutation testing are unavailable. My5-FU™ is offered by Saladax Biomedical as a laboratory-developed test; other clinical laboratories may offer in-house assays to measure 5-FU AUC.

Similarly, TheraGuide® is offered by Myriad Genetics as a laboratory-developed test; other laboratories may offer in-house assays for *DPYD* and *TYMS* mutation testing (eg, ARUP Laboratories). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing.

Both Saladax Biomedical and Myriad Genetics are CLIA-licensed laboratories.

RATIONALE:

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 dihydropyrimidine 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

Although current NCCN guidelines acknowledge that the "selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex," (41, 42) they do not recommend AUC-guided 5-FU dosing or genetic testing for *DPYD* and/or *TYMS* mutations in patients with colon, (8) rectal, (43) breast, (41) gastric, (42) or pancreatic cancer. (44)

Clinical Pharmacogenetics Implementation Consortium

The 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. (4) The guideline does not address the issue of testing.

Medicare National Coverage

There is no national coverage determination

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

81400	81401	84999	S3722

SOURCES:

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APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

Signature:_____
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Policy developed by: Medical Policy Department