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

Policy # 00291
Original Effective Date: 03/16/2011
Current Effective Date: 09/13/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers My5-FU™‡ testing or other types of assays for determining 5-fluorouracil (5-FU) area under the curve (AUC) in order to adjust 5-FU dose for colorectal cancer (CRC) patients or other cancer patients to be **investigational.***

Based on review of available data, the Company considers testing for genetic variants in dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) genes to guide 5-FU dosing and/or treatment choice in patients with cancer to be **investigational.***

Background/Overview

5-fluorouracil

The agent 5-fluorouracil is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (*TYMS*) enzyme, which is involved in DNA production. 5-fluorouracil 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 (ie, mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-fluorouracil. Several studies also have reported statistically significant positive associations between 5-fluorouracil exposure and tumor response. In current practice, however, 5-fluorouracil dose is reduced when symptoms of severe toxicity appear but is seldom increased to promote efficacy.

Based on known 5-fluorouracil pharmacology, it is possible to determine a sampling scheme for the area under the curve determination and to optimize an area under the curve target and dose-adjustment algorithm for a particular 5-fluorouracil chemotherapy regimen and patient population.

For each area under the curve value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target area under the curve without overshooting and causing severe toxicity.

In clinical research studies, 5-fluorouracil 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). My5-fluorouracil™‡ (Saladax Biomedical) and genetic testing for variants in *DPYD* and *TYMS* for predicting the risk of 5-fluorouracil toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the 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.

Rationale/Source

Variability in systemic exposure to 5-fluorouracil chemotherapy is thought to directly impact 5-fluorouracil tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-fluorouracil: (1) dosing based on the determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-fluorouracil 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-fluorouracil metabolism, respectively.

Summary of Evidence

For individuals who have cancer for whom treatment with 5-fluorouracil 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. Two studies found that the rate of severe toxicity was significantly lower in patients with metastatic colorectal cancer who received dosing using pharmacokinetic monitoring versus body surface area; however, progression free survival was not significantly different between groups. Most RCTs and nonrandomized studies comparing health outcomes were either single-center or did not use chemotherapy regimens used in current clinical practice. A systematic review of the available literature found a significantly higher response rate with body surface area based monitoring and no significant difference in toxicity. Most data derived from observational studies and the RCTs were conducted in the 1980s when different chemotherapy protocols were used. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer for whom treatment with 5-fluorouracil is indicated who receive genetic testing for variants (eg, in *DPYD* and *TYMS*) affecting 5-fluorouracil 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 TEC Assessment (2010) concluded that *DPYD* and *TYMS* variant testing had poor prognostic capacity to identify patients likely to experience severe 5-fluorouracil toxicity. Since the publication of that assessment, no prospective trials comparing the efficacy and toxicity outcomes in patients who did and did not undergo pretreatment *DPYD* and/or *TYMS* testing have been published. Three prospective observational studies used a historical control group and 1 also used a matched-pairs analysis to compare outcomes in patients who received genotype-based dosing to those who received standard dosing. No differences in overall survival, progression-free survival, or tumor progression were observed. Risk of serious toxicity was higher in *DPYD* allele carriers who received genotype-based dosing compared to wild-type patients but lower when compared to historical controls who were carriers but received standard dosing. The evidence is limited by retrospective data collection, use of historical control groups, small sample sizes, and missing data. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network Guidelines
National Comprehensive Cancer Network (NCCN) guidelines do not recommend use of area under the curve guidance for 5-fluorouracil dosing or genetic testing for *DPYD* and/or *TYMS* variants in patients with colon, rectal, breast, gastric, pancreatic cancer, or head and neck cancers.

The colon cancer guideline discusses the use of genetic testing for *DPYD* and the risk of severe toxicity after a standard dose of a fluoropyrimidine. Although the guideline discusses evidence for genetic testing for *DPYD*, it states: "However, because fluoropyrimidines are a pillar of therapy in colorectal cancer (CRC) and it is not known with certainty that given *DYPD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time."

International Association of Therapeutic Drug Monitoring and Clinical Toxicology
In 2019, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology published recommendations for therapeutic drug monitoring of 5- fluorouracil therapy.The work was supported in part by grants from the National Cancer Institute National Institutes of Health. Several authors reported relationships with Saladax, the manufacturer of the My5-fluorouracil test. The committee concluded that there was sufficient evidence to strongly recommend therapeutic drug monitoring for the management of 5-fluorouracil therapy in patients with early or advanced colorectal cancer and patients with squamous cell carcinoma of head-and-neck cancer receiving common 5-fluorouracil dosing regimens.

Clinical Pharmacogenetics Implementation Consortium
In 2009, the Clinical Pharmacogenetics Implementation Consortium was formed 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, the Clinical Pharmacogenetics Implementation Consortium published evidence-based guidelines for *DPYD* genotype and fluoropyrimidine dosing. The guidelines did not address testing.

An update to the Clinical Pharmacogenetics Implementation Consortium (2017) guidelines was published by Amstutz et al (2018). As in 2013, the primary focus of the guidelines was on the *DPYD* genotype and implications for dosing of fluoropyrimidine. In the 2017 update, the Clinical Pharmacogenetics Implementation Consortium noted that genetic testing for *DPYD* may include "resequencing of the complete coding regions" or may be confined to analysis of particular risk variants, among which Clinical Pharmacogenetics Implementation Consortium listed the c.190511G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-fluorouracil toxicity. The guideline further noted that, while other genes (*TYMS, MTHFR*) may be tested for variants, the clinical utility of such tests is yet unproven. In patients who have undergone genetic testing and who are known carriers of a *DPYD* risk variant, the guidelines recommended that caregivers strongly reduce the dosage of 5-fluorouracil-based treatments, or exclude them, depending on the patient's level of *DPYD* activity. The CPIC advised follow-up therapeutic drug monitoring to guard against underdosing and cautioned that genetic tests could be limited to known risk variants and, therefore, not identify other *DPYD* variants.

National Institute for Health and Care Excellence
In 2014, the NICE published evidence-based diagnostics guidance on the 5-fluorouracil assay for 5-fluorouracil chemotherapy dose adjustment. The evidence for the guidance was reviewed in February 2018. The guidance stated: "The My5-fluorouracil assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-fluorouracil assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
There are currently no relevant ongoing trials. Some unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
Area under the curve-guided dosing of 5-fluorouracil			
NCT00943137	The Optimisation of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer	55	June 2017
NCT02055560[a]	Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-fluorouracil Exposure Optimization Testing	350	Dec 2017 (unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 03/16/2011
Current Effective Date: 09/13/2021

03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. New Policy.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Investigational OnDose statement modified to reflect new test name, My5-FU. Investigational statement for TheraGuide testing for genetic mutations in *DPYD* or *TYMS* added. 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" to reflect incorporation of new test.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Removed TheraGuide test from policy statement as it is no longer available.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Genetic testing nomenclature updated. "Mutations" changed to "variants" throughout the policy. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2019	Coding update
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2022

Coding

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Code Type	Code
CPT	81232, 81346, 81400, 81401, 84999
HCPCS	S3722
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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