BlueCross BlueShield Federal Employee Program.

FEP 2.04.68 Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Effective Date: July 15, 2018

Related Policies: None

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

Description

Variability in systemic exposure to 5-fluorouracil (5-FU) chemotherapy 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.

FDA 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). Exome or genome sequencing tests as a clinical service are available under the auspices of 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.

POLICY STATEMENT

My5-FU™ assay testing or other types of assays for determining 5-fluorouracil (5-FU) 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*) genes to guide 5-FU dosing and/or treatment choice in patients with cancer is considered **investigational**.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic

testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACGME: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

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RATIONALE

Summary of Evidence

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-FU area under the curve, the evidence includes 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. One study, for example, found that the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring vs 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 derived from observational studies and the randomized controlled trials 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 TEC Assessment (2010) concluded that *DPYD* and *TYMS* variant testing had poor prognostic capacity to identify patients likely to experience severe 5-FU 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. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

Although current National Comprehensive Cancer Network guidelines acknowledge that the “selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex,”[30] The Network does not recommend use of area under the curve guidance for 5-fluorouracil (5-FU) dosing or genetic testing for *DPYD* and/or *TYMS* variants in patients with colon,[31] rectal,[32] breast,[30] gastric,[33] pancreatic cancer,[34] or head and neck cancers.[35]

Clinical Pharmacogenetics Implementation Consortium

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. CPIC (2013) published evidence-based guidelines for *DPYD* genotype and fluoropyrimidine dosing.[3] The guidelines did not address testing.

A 2017 update to the CPIC guidelines was published by Amstutz et al (2018).[36] As in 2013, the primary focus of the guidelines was on the *DPYD* genotype and implications for dosing of fluoropyrimidine. In the

2017 update, CPIC 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 CPIC listed the c.190511G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-FU 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-FU-based treatments, or exclude them, depending on the patient's level of *DPYD* activity. 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

The National Institute of Health and Care Excellence (2014) published evidence-based diagnostics guidance on the 5-FU assay for 5-FU chemotherapy dose adjustment.[37] 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."

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.

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POLICY HISTORY

Date	Action	Description
December 2012	New Policy	
June 2013	Update Policy	Policy updated with literature review, Reference 18 added. No change to policy statement.
June 2014	Update Policy	Policy updated with literature review; references 2, 4-7, 12, 15-16, 30-44 added; others updated and reordered. Investigational OnDose® policy statement modified to reflect new test name, My5-FU™. Investigational policy statement for TheraGuide® testing for genetic mutations in DPYD or TYMS added. Title changed to reflect information of new test.
June 2018	Update Policy	Policy updated with literature review through January 25, 2018; references 7, 22-23, 25, 27, 29-30, 36, 39-43, 47, and 52 added. “TheraGuide” removed from policy statement because this test is no longer commercially available; policy statements otherwise unchanged. Title changed to “Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer”.