BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

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

Annual Effective Policy Date: July 1, 2024

Original Policy Date: December 2012

Related Policies:

None

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

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether the use of laboratory or genetic testing improves the net health outcome by guiding 5-fluorouracil dosing and/or treatment in individuals with cancer.

POLICY STATEMENT

Assay testing for determining 5-fluorouracil area under the curve in order to adjust 5-fluorouracil dose for individuals with cancer is considered **investigational**.

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

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.

FDA REGULATORY STATUS

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). Assay testing for 5-fluorouracil blood plasma concentrations 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. The My5-FU assay is no longer marketed by Saladax Biomedical or Myriad Genetics in the United States. It is possible that therapeutic drug monitoring for 5-fluorouracil is available at a given institution as an in-house assay.

RATIONALE

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 (BSA); 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 BSA-based monitoring and no significant difference in toxicity. Most observational data were derived from studies 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.

Clinical Pharmacogenetics Implementation Consortium

In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) 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.[19,] The guidelines did not address testing.

An update to the Clinical Pharmacogenetics Implementation Consortium (2017) guidelines was published by Amstutz et al (2018).[35,] 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.1905+1G>A , c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-fluorouracil toxicity. Additional alleles potentially associated with 5-fluorouracil toxicity were added in online updates to the guideline's tables in 2020.[36,] 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.

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.[37,] The work was supported in part by grants from the National Institutes of Health National Cancer Institute. Several authors reported relationships with Saladax, the manufacturer of the My5-FU assay available in Europe. 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.

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,[38,] rectal,[39,] breast,[40,] gastric,[41,] pancreatic,[42,] or head and neck cancers.[43,]

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: "Because fluoropyrimidines are a pillar of therapy in colorectal cancer (CRC) and it is not known with certainty that given *DPYD* variants are associated with this risk and/or that dose adjustments do not impact efficacy, the NCCN Panel does not recommend universal pretreatment *DPYD* genotyping at this time."

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2012	New policy	
June 2013	Replace policy	Policy updated with literature review, Reference 18 added. No change to policy statement.
June 2014	Replace 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	Replace 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€š 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€š.
June 2019	Replace policy	Policy updated with literature review through January 9, 2019; no references added. Policy statements unchanged.
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through January 22, 2020; references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through February 2, 2021; reference added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through January 24, 2022; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through January 31, 2023; references added. "My 5-fluorouracil€ž" removed from policy statement because this test is no longer commercially available in the U.S. Minor editorial refinements to policy statements; intent unchanged.
June 2024	Replace policy	Policy updated with literature review through January 12, 2024; reference added. Policy statements unchanged.