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 the determined area under the curve (AUC) 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.
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-FU dosing and/or treatment in patients with cancer.

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

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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>
### 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

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

## BENEFIT APPLICATION

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).

## 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. My5-FU™ (Saladax Biomedical) and genetic testing for variants in DPYD and TYMS for predicting the risk of 5-FU toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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

### Summary of Evidence

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-FU AUC, the evidence includes RCTs, observational studies, and systematic reviews. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, and treatment-related morbidity. Several analyses of patients with CRC have evaluated clinical validity. One study, for example, found the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring vs 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 derived 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.

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For individuals who have cancer for whom treatment with 5-FU is indicated who receive genetic testing for variants (e.g., in DPYD and TYMS) affecting 5-FU metabolism, the evidence includes observational studies and systematic reviews. The relevant outcomes are OS, 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. Three prospective observational studies used a historical control group and one 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 OS, 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 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."32 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,33 rectal,34 breast,32 gastric,35 pancreatic cancer,36 or head and neck cancers.37

Clinical Pharmacogenetics Implementation Consortium

The CPIC (2009) 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. The CPIC (2013) published evidence-based guidelines for DPYD genotype and fluoropyrimidine dosing.3 The guidelines did not address testing.

An update to the CPIC (2017) guidelines was published by Amstutz et al (2018).38 As in 2013, the primary focus of the guidelines was on the DPYD genotype and implications for dosing of fluoropyrimidine. In the update, the CPIC (2017) 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 under-dosing 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.39 The guidance stated: “The My5-FU assay is only recommended for use in research for guiding

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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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**REFERENCES**


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25. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer. TEC Assessments. 2010;24:Tab 13.


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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2012</td>
<td>New policy</td>
<td>Policy updated with literature review. Reference 18 added. No change to policy statement.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>June 2018</td>
<td>Replace policy</td>
<td>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”.</td>
</tr>
<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through January 9, 2019; no references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 29, 2019; references added. Policy statements unchanged.</td>
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