Protocol

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

(20468)

Medical Benefit

<table>
<thead>
<tr>
<th>Effective Date: 08/01/19</th>
<th>Next Review Date: 05/20</th>
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Preauthorization

<table>
<thead>
<tr>
<th>No</th>
<th>Review Dates: 05/19</th>
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This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals: • With cancer for whom treatment with 5-fluorouracil is indicated</td>
<td>Interventions of interest are: • Laboratory assays to determine 5-fluorouracil area under the curve</td>
<td>Comparators of interest are: • Standard dosing of 5-fluorouracil</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With cancer for whom treatment with 5-fluorouracil is indicated</td>
<td>Interventions of interest are: • Genetic testing for variants (e.g., in DPYD and TYMS) affecting 5-fluorouracil metabolism</td>
<td>Comparators of interest are: • Standard dosing without genetic testing</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Treatment-related morbidity</td>
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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.

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 randomized controlled trials, observational studies, and systematic reviews. The 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 versus body surface area monitoring but pro-
Regression-free survival did not differ between groups in patients with stage IV or recurrent cancer. No randomized controlled trials 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 body surface area-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 (e.g., in DPYD and TYMS) affecting 5-FU metabolism, the evidence includes observational studies and systematic reviews. The 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.

POLICY

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 protocol updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Genome 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</td>
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Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

5-FLUOROURACIL

The agent 5-FU is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (TYMS) enzyme, which is involved in DNA production. 5-FU has been used for many years to treat solid tumors (e.g., colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 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 the area under the curve (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.

Measuring Exposure to 5-FU

Laboratory Testing

Patient exposure to 5-FU is most accurately described by estimating the AUC, the total drug exposure over a defined period of time. 5-FU exposure is influenced by the method of administration, circadian variation, liver function, and the presence of inherited dihydropyrimidine reductase (DPYD)-inactivating genetic variants that can greatly reduce or abolish 5-FU catabolism. As a result, both inter- and intrapatient variability in 5-FU plasma concentration during administration is high.
Determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the United States, a commercial immunoassay (My5-FU) can quantify plasma 5-FU concentration from a blood sample drawn during continuous infusion at steady state (18-44 hours after the start of infusion) and provide a dose-adjustment algorithm to maintain plasma 5-FU AUC between 20 and 30 mg/h/L during the next cycle.\(^1\)

**Genetic Testing**

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.\(^2\) For example, 5-FU clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic variants in DPYD, located on chromosome one, can lead to reduced 5-FU catabolism and increased toxicity. Many variants have been identified (e.g., IVS14+1G>A [also known as DPYD*2A], 2846A>T [D949V]). DPYD deficiency is an autosomal codominantly inherited trait.\(^3\)

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.\(^4\) Genetic variants in TYMS can cause tandem repeats in the TYMS enhancer region (TSER). One variant leads to three tandem repeats (TSER*3) and has been associated with 5-FU resistance due to increased tumor TYMS expression compared with the TSER*2 variant (two tandem repeats) and wild-type forms.

**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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**
REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


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.


