Protocol

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

(20468)

Medical Benefit		**Effective Date**: 08/01/19	**Next Review Date**: 05/21
Preauthorization	No	**Review Dates**: 05/19, 05/20	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer for whom treatment with 5-fluorouracil is indicated	Interventions of interest are: • Laboratory assays to determine 5-fluorouracil area under the curve	Comparators of interest are: • Standard dosing of 5-fluorouracil	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Treatment-related morbidity
Individuals: • With cancer for whom treatment with 5-fluorouracil is indicated	Interventions of interest are: • Genetic testing for variants (e.g., in DPYD and TYMS) affecting5-fluorouracil metabolism	Comparators of interest are: • Standard dosing without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Treatment-related morbidity

DESCRIPTION

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. One study, for example, found that the rate of severe toxicity was signifi-

cantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring versus body surface area 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-fluorouracil dose adjustment using the My 5-fluorouracil 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 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.

For individuals who have cancer for whom treatment with 5-fluorouracil is indicated who receive genetic testing for variants (e.g., 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 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 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 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 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

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

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-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 (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-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.

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). 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.

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

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