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Corporate Medical Policy

Testing for 5-Fluorouracil Use in Cancer Patients AHS-M2067

File Name:	testing_for_5_fluorouracil_use_in_cancer_patients
Origination:	1/2019
Last CAP Review	8/2020
Next CAP Review:	8/2021
Last Review:	10/2020

Description of Procedure or Service

Chemotherapeutic agents are incredibly potent drugs, often carrying cytotoxic side effects. Most chemotherapeutic drugs have a steep dose-response relationship and a narrow therapeutic index (a range where an agent provides therapeutic effect without major side effects). Identification of the optimal dose of a chemotherapeutic agent, such as 5-fluorouracil, has been proposed as a potential improvement for the management of cancer patients (Eaton, 2019).

This policy does not address pharmacogenetic testing to aid or direct chemotherapies. For pharmacogenetic testing, please refer to AHS-M2021.

Related Policies:
Pharmacogenetic Testing AHS-M2021

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Testing for 5-fluorouracil use in cancer patients is not covered. BCBSNC will not reimburse for non-covered services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Testing for 5-Fluorouracil Use in Cancer Patients is covered

Not applicable.

When Testing for 5-Fluorouracil Use in Cancer Patients is not covered

Reimbursement is not allowed for testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer.

Reimbursement is not allowed for assays for determining 5-fluorouracil area under the curve in order to adjust 5-FU dosing for cancer patients, including but not limited to My5-FU.

Reimbursement is not allowed for uracil breath tests and dihydrouracil/uracil ratio testing of plasma, serum, or urine samples *to aid in managing dose adjustment in individuals undergoing 5-fluorouracil chemotherapy.*

Policy Guidelines

DPYD is a gene which encodes dihydropyrimidine dehydrogenase (DPD). Variants in this gene are associated with increased toxicity to fluorouracil. "The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), an enzyme that catalyzes the rate-limiting step in fluorouracil metabolism. Individuals who carry at least one copy of no function *DPYD* variants, such as *DPYD*2A*, may not be able to metabolize fluorouracil at normal rates, and are at risk of potentially life-threatening fluorouracil toxicity, such as bone marrow suppression and neurotoxicity. The prevalence of DPD deficiency in Caucasians is approximately 3%-5%" (Dean, 2016).

Mutations can range from a decreased level of functional dihydropyrimidine dehydrogenase to a complete absence. Mutations that result in the absence of DPD are associated with more severe signs and symptoms compared to mutations that lead to a partial deficiency of this enzyme (DHHS, 2017).

Clinical Validity and Utility

Krishnamurthi (2017) stated, "there are no accepted guidelines for management of patients who are identified as having a high or moderate risk for toxicity according to TYMS [thymidylate synthetase] variants. Any patient who experiences severe toxicity following FU treatment will require a significant dose reduction if treatment will continue. Patients who have unusually severe toxicity or severe toxicity within days after dosing with a fluoropyrimidine should be suspected of having an at-risk DPYD or TYMS mutation. Testing for at-risk mutations in DPYD and TYMS is reasonable in these patients, as dosing recommendations for DYPD mutation carriers are available from CPIC, and because identification of at-risk mutations may be of use if family members are to be treated in the future with fluoropyrimidines."

Krishnamurthi (2017) further stated that "testing is commercially available that might identify patients who are at risk for severe toxicity from fluoropyrimidines based upon DPYD and TYMS genotype. Some authors suggest that testing should ideally be carried out before initiation of treatment to identify high-risk patients; however, this is a controversial area, and this approach has not been widely adopted. Although genotyping may identify a small fraction of patients for whom serious toxicity is a concern, most patients who develop serious toxicity to fluoropyrimidines do not have mutations in either DPYD or TYMS (ie, sensitivity is limited). Furthermore, the frequency of high-risk alleles in the general population is quite small (mostly <1 percent), and many patients who inherit these polymorphisms will not suffer from undue toxicity (ie, the positive predictive value has been variable). For these reasons, we generally reserve genotyping for those patients who have unexpected toxicity (myelosuppression, mucositis, diarrhea, neurotoxicity, cardiotoxicity) during the first few cycles of fluoropyrimidine therapy."

Yang et al (2016) conducted a meta-analysis of data from 2 RCTs and 3 observational studies (654 patients) to compare the efficacy and toxicity of the use of pharmacokinetic (PK)-guided versus Body Surface Area (BSA)-based dose adjustment of 5-FU in advanced cancers. PK-monitored 5-FU therapy was associated with significant improvement in overall response rate (odds ratio = 2.04, 95% confidence interval, 1.41-2.95, Z = 3.78, P = 0.0002) compared with the traditional BSA method. The researchers concluded that "in comparison with conventional BSA method, PK-based 5-FU dosage confirmed a superior overall response rate and improved toxicities irrespective of significant difference, the results of which indicated that PK- monitored 5-FU dosage has the potential to be performed in colorectal cancer personalized therapy."

Gamelin et al (2008) conducted a multicenter, randomized study to compare conventional dosing of fluorouracil with pharmacokinetically guided FU dose adjustment in terms of response, tolerability, and survival. 208 patients with measurable metastatic colorectal cancer were randomly assigned to two groups: group A (104 patients; 96 assessable), in which the FU dose was calculated based on body-surface area; and group B (104 patients; 90 assessable), in which the FU dose was individually determined using pharmacokinetically guided adjustments. Patients that received FU dose adjustment based on pharmacokinetic monitoring showed significantly improved objective response rate, a trend to higher

survival rate, and fewer grade 3/4 toxicities. The researchers concluded that "these results support the value of pharmacokinetically guided management of FU dose in the treatment of metastatic colorectal patients."

State and Federal Regulations, as applicable

Prescribing Information for fluorouracil contains a warning that states the following:
"Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil.
Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test (FDA, 2016)."
No test has been FDA approved to measure DYPD activity or detect DYPD mutations. All tests are considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.
LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).
As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) (Beumer et al., 2019)

The IATDMCT released guidelines on the dosing of 5-FU. With regards to assessing systemic exposure to 5-FU, the IATDMCT noted that area-under-curve (AUC) was the "accepted and clinically relevant" metric. They also noted that a relationship existed between 5-FU AUC and clinical activity (as well as toxicity. They go on to state, "It should be noted that statistically significant correlations between 5- FU exposure and toxicity have been observed across several disease types (squamous cell carcinoma of the head and neck (SCCHYN), nasopharyngeal cancer, and CRC), disease settings (metastatic, locally advanced), and dosing types (bolus, infusion)." Also, they note that "several clinical studies…have found statistically significant correlations between 5-FU exposure and clinical outcome, mostly with response rates being the metric, but also indicated by overall survival" (Beumer et al., 2019; NICE, 2014).

The IATDMCT also made remarks on the use of TDM for 5-FU. They noted that TDM reduced variability and toxicity, as well as improved clinical activity in patients receiving 5-FU, and "strongly recommend" TDM for the management of 5-FU therapy in patients with colorectal or head-and-neck cancer receiving common 5-FU regimens (Beumer et al., 2019). Concerning the use of the uracil breath test, the IATDMCT states, "The uracil breath test does not help in determining the correct does and is not recommended for clinical use" (Beumer et al., 2019).

National Comprehensive Cancer Network (NCCN) (NCCN, 2020a, 2020b, 2020c)

The NCCN published guidelines on management of antiemesis, intended to control one of chemotherapy's primary side effects. In it, the only chemotherapeutic agent listed with an AUC-based dosing regimen is carboplatin. 5-FU, docetaxel, and paclitaxel are listed as having 10-30% emetic risk whereas imatinib is listed as <30% risk. No information regarding therapeutic drug monitoring was

included (NCCN, 2020a). Furthermore, the NCCN did not address TDM in either its colon cancer or head and neck cancer guidelines (NCCN, 2020b, 2020c).

National Institute for Health and Care Excellence (NICE) (NICE, 2014, 2017)

NICE remarked that the My5-FU assay should only be recommended for research purposes, although they noted that it has "promise" (NICE, 2014). In a December 2017 review of the 2014 guideline, NICE stated that no changes were required (NICE, 2017).

Clinical Pharmacogenetics Implementation Consortium (CPIC) (Amstutz et al., 2018)

In 2017, the CPIC published updated guidance on dihydropyrimidine dehydrogenase (DPYD) genotyping and fluoropyrimidine (5-FU) dosing. The following recommendations are related to TDM:
• "In DPYD poor metabolizers (DPYD-AS: 0.5 or 0), it is strongly recommended to avoid use of 5-fluorouracil containing regimens. However, if no fluoropyrimidine-free regimens are considered a suitable therapeutic option, 5-fluorouracil administration at a strongly reduced dose combined with early therapeutic drug monitoring may be considered for patients with DPYD-AS of 0.5. It should be noted, however, that no reports of the successful administration of low dose 5-fluorouracil in DPYD poor metabolizers are available to date."
• "Pharmacokinetically-guided dosing of 5-fluorouracil has been shown to result in an increase in the proportion of patients with 5-fluorouracil exposure (AUC) within the targeted therapeutic range and a reduced number of 5-fluorouracil related adverse effects. In particular, to avoid underdosing of patients with genotype-based dose reductions who tolerate higher 5-fluorouracil doses, follow-up therapeutic drug monitoring is recommended."
• For DPYD intermediate metabolizers, the following dosing recommendation was given: "Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available)."
• For DPYD poor metabolizers, the following dosing recommendation was given: "In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dosed with early therapeutic drug monitoring" (Amstutz et al., 2018).

Therapeutic Pharmacological Monitoring and Personalization of Treatments (STP-PT) Group of The French Society of Pharmacology and Therapeutics (SFPT) and the Groupe de Pharmacologie Cinique Oncologique (GPCO) (Lemaitre et al., 2018).

The STP-PT group of the SFPT and GPCO on 5-FU therapeutic drug monitoring state that "based on the latest and most up-to-date literature data, [we] recommend the implementation of 5-FU Therapeutic Drug Monitoring in order to ensure an adequate 5-FU exposure" (Lemaitre et al., 2018.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 80299, 82542, 83789, S3722

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: Genetic Testing for 5-Fluorouracil Use in Cancer Patients

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Specialty Matched Consultant Advisory Panel 8/2019

For Policy Titled: Testing for 5-Fluorouracil Use in Cancer Patients

Medical Director review 11/2019

Specialty Matched Consultant Advisory Panel 8/2020

Medical Director review 10/2020

Policy Implementation/Update Information

For Policy Titled: Genetic Testing for 5-Fluorouracil Use in Cancer Patients

1/1/2019 New policy developed. Genetic testing for 5 fluorouracil use in cancer patients is considered **investigational**. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

4/16/19 Revised coding table under "Billing/Coding" section. (lpr)

10/1/19 Specialty Matched Consultant Advisory Panel review 8/21/19. Deleted coding table from Billing/Coding section. No change to policy intent. Medical Director review 8/2019. (lpr)

For Policy Titled: Testing for 5-Fluorouracil Use in Cancer Patients

12/10/19 Reviewed by Avalon 3rd Quarter 2019 CAB. **Policy title changed from "Genetic Testing for 5-Fluorouracil Use in Cancer Patients" to "Testing for 5-Fluorouracil Use in Cancer Patients."** Added the following statement to "When Not Covered" section: Uracil breath tests and dihydrouracil/uracil ratio testing of plasma, serum, or urine samples *to aid in managing dose adjustment in individuals undergoing 5-fluorouracil chemotherapy are* considered **investigational.** Medical Director review 11/2019**.** (lpr)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. Literature review. Updated policy guidelines section and references. Deleted CPT codes 81232, 81346 and added CPT codes 80299, 82542, 83789 to Billing/Coding section. Medical Director review 10/2020. (lpr)