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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: 1/1/2019
Last CAP Review: 8/2019
Next CAP Review: 8/2020
Last Review: 12/2019

Description of Procedure or Service

5-Fluorouracil (5-FU) is a chemotherapeutic agent that belongs to the drug class of fluoropyrimidines. It is used in the treatment of cancers of the breast, colon, rectum, stomach, and pancreas (Dean, 2016; NCI, 2017).

Dihydropyrimidine dehydrogenase (DPD), is rate-limiting enzyme for fluoropyrimidine catabolism. Numerous genetic variants in DPYD, the gene encoding DPD, are known that alter the protein sequence or mRNA splicing. Some of these variants, do not affect DPD activity in a clinically relevant manner, whereas others result in reduced enzyme function (U. Amstutz et al., 2018) and increased toxicities including grade 3/4 neutropenia, diarrhea and stomatitis (Cremolini et al., 2018).

***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 considered investigational for all applications. BCBSNC does not provide coverage for investigational 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

Testing for genetic mutations in dihydropyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.

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, are considered investigational.
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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.

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
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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.”

In 2016 Meulendijks et al concluded that “In patients intended for treatment with fluoropyrimidine-based chemotherapy, DPD status should be determined prior to start of therapy in order to identify patients at high risk of severe and potentially fatal toxicity. At present, clinical validity is well established for four DYPD variants (DPYD*2A, c.2846A > T, c.1679T > G, and c.1236G > A/Haplotype B3), and upfront screening for these variants and genotype-guided dose adjustment is recommended (Caudle et al., 2013; Henricks et al., 2015). Other DYPD variants have been associated with DPD deficiency (Offer et al., 2014; Offer, Wegner, Fossum, Wang, & Diasio, 2013), but additional clinical translational investigations are required before recommending dose adjustment in patients carrying these variants. Genotyping of rs895819 in MIR27A has strong potential to increase sensitivity and PPV of upfront screening and thereby improve patient selection (Ursula Amstutz et al., 2015; Meulendijks et al., 2016), but additional validation studies are desirable. The DPD phenotyping tests, in general, require further validation of clinical validity and utility.”

Cremolini et al published a large study in which 443 (87%) out of 508 metastatic colorectal cancer patients were tested for DPYD and UGT1A1 variants before first-line 5-fluorouracil- and irinotecan-based chemotherapy regimens. UGT1A1 encodes for a UDP-glucuronosyltransferase enzyme. Results showed that patients bearing DPYD c.1905+1G/A and c.2846A/T genotypes, together with UGT1A1*28 variant carriers, have an increased risk of experiencing clinically relevant toxicities, including hematological AEs and stomatitis. No carrier of the DPYD c.1679T>G minor allele was identified. Present results support the preemptive screening of mentioned DPYD and UGT1A1 variants to identify patients at risk of clinically relevant 5-fluorouracil- and irinotecan-related AEs, in order to improve treatments’ safety through a “genotype-guided” approach (Cremolini et al., 2018).

Variants in thymidylate synthase (TYMS) are also associated with increased risk of fluoropyrimidine toxicity. However, data are less certain than with DPYD, and there are no accepted guidelines for management of patients identified as increased risk for toxicity according to TYMS variants (Krishnamurthi, 2017).

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

Clinical Pharmacogenetics Implementation Consortium (CPIC) Dosing Guidelines (2018) for fluoropyrimidines (i.e. 5-fluorouracil, capecitabine or tegafur) stated that:
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“CPIC recommends an alternative drug for patients who are homozygous for DPYD non-functional variants - *2A (rs3918290), *13 (rs55886062), and rs67376798 A (on the positive chromosomal strand) - as these patients are typically DPD deficient. Consider a 50% reduction in starting dose for heterozygous patients (intermediate activity).”

The 2013 CPIC guidelines stated that “patients who are heterozygous for the nonfunctional DPYD variants mostly demonstrate partial DPD deficiency. Thus, our recommendation is to start with at least a 50% reduction of the starting dose; followed by an increase in dose in patients experiencing no or clinically tolerable toxicity, to maintain efficacy; and a decrease in dose in patients who do not tolerate the starting dose, to minimize toxicities” (Caudle et al, 2013). For patients who are homozygous for DPYD*2A, *13, or rs67376798 and may demonstrate complete DPD deficiency, CPIC stated that “the use of 5-fluorouracil or capecitabine is not recommended in these patients.”

National Comprehensive Cancer Network

The 2018 NCCN Guidelines for colon cancer continue to state that: Universal pretreatment DYPD genotyping remains controversial, and the NCCN Panel does not support it at this time.

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: 81232, 81346, 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

Policy Implementation/Update Information

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

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1/1/2019  New policy developed. Genetic testing for 5 fluorouracil use in cancer patients is considered investigative. 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 investigative. Medical Director review 11/2019. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.