

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>LABORATORY AND GENETIC TESTING FOR USE OF 5-FLUOROURACIL IN PATIENTS WITH CANCER</b>
<b>POLICY NUMBER</b>	<b>MP 2.354</b>

<b>CLINICAL BENEFIT</b>	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
<b>Effective Date:</b>	<b>4/1/2024</b>

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### I. POLICY

Assay testing for determining 5-fluorouracil area under the curve in order to adjust 5-fluorouracil (5-FU) dose for individuals with cancer 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 individuals with cancer is considered **investigational**.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with the above procedures.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

### Policy Guidelines

#### GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations. These recommendations primarily apply to

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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
<b>Mutation</b>	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.

**Cross-reference:**

NA

## II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

**FEP PPO** - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

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<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

### III. DESCRIPTION/BACKGROUND

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#### 5-FLUOROURACIL

The agent 5-fluorouracil (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 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.

#### REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Assay testing for 5-fluorouracil blood plasma concentrations and genetic testing for variants in *DPYD* and *TYMS* for predicting risk of 5-fluorouracil toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by 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. The My5-FU assay is no longer marketed by Saladax Biomedical or Myriad Genetics in the United States. It is possible that therapeutic drug monitoring for 5-FU is available at a given institution as an in-house assay.

### IV. RATIONALE

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#### 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 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

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patients with colorectal cancer have evaluated clinical validity. Two studies found that the rate of severe toxicity was significantly lower in patients with metastatic colorectal cancer who received dosing using pharmacokinetic monitoring versus body surface area; however, progression free survival was not significantly different between groups. Most RCTs and nonrandomized studies comparing health outcomes were either single-center or did not use 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 that the technology results in an improvement in the net health outcome.

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. 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. Three prospective observational studies used a historical control group and 1 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

**V. DEFINITIONS**

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NA

**VI. BENEFIT VARIATIONS**

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

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### VII. DISCLAIMER

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*Capital Blue Cross’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member’s plan of benefits, please contact Capital Blue Cross’ Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

### VIII. CODING INFORMATION

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**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Investigational; therefore not covered:**

Procedure Codes							
S3722	81232	81346	84999				

### IX. REFERENCES

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### X. POLICY HISTORY

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<b>MP 2.354</b>	<b>12/29/17</b> New policy adopting BCBSA. Testing is considered investigational. Coding Reviewed
	<b>9/28/18 Admin update.</b> Coding reviewed and updated.
	<b>1/14/19</b> Consensus review. No change to the policy statements. References updated. Rationale revised. Appendix removed.
	<b>2/4/20 Consensus review.</b> No change to policy statements. References updated, coding reviewed.
	<b>1/14/21 Consensus review.</b> No change to policy statements. References updated.
	<b>4/15/2022 Consensus review.</b> No change to policy statements. Added NCCN statement. Updated FEP, rationale, and references. No coding changes.
	<b>4/20/2023 Consensus review.</b> "My 5-fluorouracil™" was removed from the policy statement because this test is no longer commercially available in the U.S. Minor editorial refinements to policy statements; intent unchanged. Updated regulatory status, and references. No coding changes.

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