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FEP Medical Policy Manual

FEP 2.04.68 Laboratory and Genetic Testing for Use of Fluoropyrimidine Therapy in Individuals With Cancer

Annual Effective Policy Date: July 1, 2026

Original Policy Date: December 2012

Related Policies:

None

Laboratory and Genetic Testing for Use of Fluoropyrimidine Therapy in Individuals With Cancer

Description

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5-fluorouracil and Xeloda (converts to 5-FU in vivo) belong to the drug class fluoropyrimidine, and are used as chemotherapies. 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.

OBJECTIVE

The objective of this evidence review is to determine whether the use of laboratory or genetic testing improves the net health outcome by guiding fluoropyrimidine (5-FU and Xeloda) dosing and/or treatment in individuals with cancer.

POLICY STATEMENT

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

One time germline testing for genetic variants in the dihydropyrimidine dehydrogenase (*DPYD*) gene to guide initial fluoropyrimidine (i.e. 5-fluorouracil, Xeloda) dosing or fluoropyrimidine as a treatment choice in individuals with certain cancers may be considered **medically necessary**.

Testing for genetic variants in thymidylate synthase (*TYMS*) genes to guide 5-fluorouracil dosing and/or treatment choice in individuals with cancer is considered **investigational**.

POLICY GUIDELINES

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

CANCER TYPES:
The FDA labels for fluorouracil (5-FU) and Xeloda include cancer types: colorectal, breast, gastric, esophageal, and pancreatic. The National Comprehensive Cancer Network (NCCN) guidelines that address testing for *DPYD* variants prior to use of fluoropyrimidine therapy are shown in Table 1 below and are 2A recommendations. Additional cancer types use fluoropyrimidine therapy, but the NCCN guidelines for those other cancer types do not as yet address testing for *DPYD* variants.

OTHER FLUOROPYRIMIDINES:
The Clinical Pharmacogenetics Implementation Consortium (CPIC) information in the Supplemental Information Section includes tegafur, which is an oral prodrug for 5-fluorouracil (5-FU) primarily used in combination with other agents (tegafur-Uracil UFT or Tegafur/gimeracil/oteracil S-1). There are a few historical references to tegafur in NCCN. However, tegafur is not FDA-approved and thereby not addressed in this reference medical policy.

TEST METHODOLOGIES:
While a specific test is not recommended in the FDA labels for 5-FU or Xeloda, dihydropyrimidine dehydrogenase deficiency can be tested using using polymerase chain reaction (PCR) for targeted variant analysis or using next-generation sequencing (NGS) of the coding regions of the *DPYD* gene. The FDA labels acknowledge the following variants although note that this is not a complete list of variants with the potential for dihydropyrimidine dehydrogenase deficiency: c.1905+1G>A (DPYD *2A), c.1679T>G (DPYD *13), c.2846A>T, c.1129-5923C>G (Haplotype B3).

Per the NCCN colon cancer guideline, the 4 most common and best characterized variants are: c.1905+1G>A, c.1679T>G, c.2846A>T, and c.1236G>A.[1,]

The difference between FDA and NCCN then is in c.1129-5923C>G and c.1236G>A. A 2024 consensus recommendation from major pharmacogenomics groups identifies that some laboratories test the synonymous variant c.1236G>A, and not the intronic splice variant c.1129 - 5923C>G, to predict an individual"s risk of severe fluoropyrimidine-related toxicity; and, point out that c.1129 - 5923C>G and c.1236G>A are not in perfect linkage disequilibrium. Using c.1236G>A then may not predict an accurate phenotype in rare cases.[2,] Although rare, the consensus addresses the importance of assaying for the functional variant that causes decreased activity (ie, c.1129 - 5923C>G).

The joint consensus identifies the following Tier 1 *DPYD* variants: c.1905+1G>A, c.1679T>G, c.1129 - 5923C>G, c.1236G>A, c.557A>G, c.868A>G, c.2279C>T, and c.2846A>T.[2,] Tier 1 variants refer to *DPYD* variants that meet all 4 of the following criteria: they have well-characterized effects on DPD enzyme function, occur at an appreciable allele frequency in at least one human population, have reference materials, and are technically feasible for detection using standard clinical molecular testing methods.

The American Society of Clinical Oncology (ASCO) has reaffirmed the necessity of pre-treatment testing for dihydropyrimidine dehydrogenase (DPD) deficiency via *DPYD* genotyping for all individuals receiving fluoropyrimidines. While guidelines are forthcoming, ASCO relies on a review that suggests clinicians should follow: FDA recommendations to incorporate pretreatment *DPYD* testing, Association for Molecular Pathology (AMP) recommendations to select a comprehensive *DPYD* test, and original Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations regarding appropriate fluoropyrimidine dosing to reduce preventable severe and fatal toxicities in individuals receiving systemic fluoropyrimidine chemotherapy.[3,4,]

Targeted variant testing using polymerase chain reaction and sequence analysis of the entire coding region using next-generation sequencing are both offered by various labs within the United States. While sequencing would be expected to identify more variants, it would have longer turn around time to results and results would include variants of uncertain significance with unknown clinical utility. For more information, see: National Institutes of Health (NIH). Genetic Testing Registry (GTR). Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2012 - present. Available from: https://www.ncbi.nlm.nih.gov/gtr/.

Table 1. NCCN Guideline Recommendations for DPYD Variant Testing.

Guideline - Disease	NCCN Recommendation
Ampullary Adenocarcinoma (V2.2026)	For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Anal Carcinoma (V1. 2026)	FDA added a Boxed warning to the Xeloda label, recommending to test individuals for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary. For information on DPYD testing and fluoropyrimidine-associated toxicity, see the NCCN Guidelines for Colon Cancer.
Appendiceal Neoplasms and Cancers (V1. 2026)	FDA added a Black Box warning to the Xeloda label, recommending to test individuals for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary. For information on DPYD testing and fluoropyrimidine-associated toxicity, see the NCCN Guidelines for Colon Cancer.
Breast Cancer - Invasive Breast Cancer (V1. 2026)	The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual individual variability, prior treatment, and comorbidities. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in individuals with cancer. For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer.
Cervical Cancer (V2. 2026)	Testing for dihydropyrimidine dehydrogenase (DPYD) genetic variants should be considered prior to fluoropyrimidine therapy. After discussions regarding risk assessment, individuals may choose DPYD genetic testing. However, no specific test is recommended at this time and there are insufficient data to inform dose adjustments for many of the DPYD variants. See NCCN Guidelines for Colon Cancer (COL-1 2 of 3) for more information,.
Colon Cancer (V5. 2025)[a]	FDA added a Boxed warning, recommending to test individuals for genetic variants of *DPYD* prior to initiating capecitabine or fluorouracil unless immediate treatment is necessary. Furthermore, use should be avoided in individuals with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency. However, no specific test is recommended and there are insufficient data to inform dose adjustments for many of the *DPYD* variants. See Principles of Pharmacogenetics (COL- I) and DPYD Testing and Fluoropyrimidine- Associated Toxicity Discussion section for more information.
Esophageal and Esophagogastric Junction Cancers (V2. 2026)	For more information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Gastric Cancer (V2. 2026)	For more information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Head and Neck Cancers (V1. 2026)	For more information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Head and Neck Cancers - Cancer of the Nasopharynx (V1. 2026)	For more information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Occult Primary (V1. 2026)	For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer
Penile Cancer (V1. 2026)	For more information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer.
Rectal Cancer (V4. 2025)	Rectal cancer without suspected or proven distant metastases Or, Rectal cancer with suspected or proven distant metastases. FDA added a Black Box warning to the Xeloda label, recommending to test individuals for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary. For information on DPYD testing and fluoropyrimidine-associated toxicity, see the NCCN Guidelines for Colon Cancer.
Small Bowel Adenocarcinoma (V1.2026)	Clinical location: duodenum, jejunum/ileum. FDA added a Boxed warning to the Xeloda label, recommending to test individuals for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary. For information on DPYD testing and fluoropyrimidine-associated toxicity, see the NCCN Guidelines for Colon Cancer.

Adapted from NCCN Biomarkers Compendium. https://www.nccn.org/compendia-templates/compendia/biomarkers-compendium

[a]The V5.2025 version of the NCCN Colon Cancer Guidelines does not yet reflect the labeling updates to Xeloda and fluorouracil products resulting from the February 5, 2026 FDA safety labeling update.[FDA. Safety labeling update for Xeloda and f.... ne Accessed February 19, 2026.]

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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). Assay testing for 5-fluorouracil blood plasma concentrations 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. 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-fluorouracil is available at a given institution as an in-house assay.

Food and Drug Administration Labeling on Pharmacogenomic Test for Fluoropyrimidines (5-FU and Xeloda)

The FDA has included pharmacogenomics information in the physician prescribing information of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, the FDA has given clear directives on use of pharmacogenomic testing for 5-FU and Xeloda. As the information in the labels for Xeloda and 5-fluorouracil is identical in terms of *DPYD* testing, they are grouped below:

FDA Boxed Warning Xeloda and 5-FU:

- Serious adverse reactions or death may occur in individuals with complete DPD deficiency.
- Test individuals for genetic variants of *DPYD* prior to initiating Xeloda/5-FU unless immediate treatment is necessary.
- Avoid use of Xeloda/5-FU in individuals with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency.

FDA Dosage and Administration Xeloda and 5-FU:

- Prior to initiating Xeloda/5-FU, test individuals for genetic variants of the *DPYD* gene unless immediate treatment is necessary.
- An FDA-authorized test for the detection of the *DPYD* gene to identify individuals at risk of serious adverse reactions with Xeloda/5-FU is not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).
- Avoid use of Xeloda/5-FU in individuals known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency.
- No Xeloda/5-FU dose has been proven safe for individuals with complete DPD deficiency. For individuals with partial DPD deficiency, individualize the dosage and modify based on tolerability and intent of treatment.

RATIONALE

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 individuals with colorectal cancer have evaluated clinical validity. Two studies found that the rate of severe toxicity was significantly lower in individuals with metastatic colorectal cancer who received dosing using pharmacokinetic monitoring versus body surface area (BSA); 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 BSA-based monitoring and no significant difference in toxicity. Most observational data were derived from studies 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 fluoropyrimidine is indicated who receive genetic testing for variants in *DPYD* that affect 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. No prospective trials comparing efficacy and toxicity outcomes in individuals who did and did not undergo pretreatment *DPYD* 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 individuals 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 individuals, 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 updated review relies on the U.S. Food and Drug Administration -approved labels for 5-fluorouracil and Xeloda that include clear directives on use of pharmacogenomic testing. Evidence for these indications was not further evaluated.

For individuals who have cancer for whom treatment with 5-fluorouracil is indicated who receive genetic testing for variants in *TYMS* that affect 5-fluorouracil metabolism, no studies were identified. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. Prospective trials comparing efficacy and toxicity outcomes in individuals who did and did not undergo pretreatment *TYMS* testing are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Clinical Pharmacogenetics Implementation Consortium

In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB, an internet research tool developed by Stanford University, and the Pharmacogenomics Research Network of the National Institutes of Health. In 2013, the Clinical Pharmacogenetics Implementation Consortium published evidence-based guidelines for *DPYD* genotype and fluoropyrimidine dosing.[26,] The guidelines did not address testing.

An update to the Clinical Pharmacogenetics Implementation Consortium (2017) guidelines was published by Amstutz et al (2018).[39] As in 2013, the primary focus of the guidelines was on the *DPYD* genotype and implications for dosing of fluoropyrimidine. In the 2017 update, the Clinical Pharmacogenetics Implementation Consortium noted that genetic testing for *DPYD* may include "resequencing of the complete coding regions" or may be confined to analysis of particular risk variants, among which Clinical Pharmacogenetics Implementation Consortium listed the c.1905+1G>A , c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-fluorouracil toxicity. Additional alleles potentially associated with 5-fluorouracil toxicity were added in online updates to the guideline's tables in 2020.[40] The guideline further noted that, while other genes (*TYMS, MTHFR*) may be tested for variants, the clinical utility of such tests is yet unproven. In individuals who have undergone genetic testing and who are known carriers of a *DPYD* risk variant, the guidelines recommended that caregivers strongly reduce the dosage of 5-fluorouracil-based treatments, or exclude them, depending on the individual"s level of *DPYD* activity. The CPIC advised follow-up therapeutic drug monitoring to guard against underdosing and cautioned that genetic tests could be limited to known risk variants and, therefore, not identify other *DPYD* variants. In 2024, another online update was published, stating that some case reports had reported evidence for a potentially reduced treatment effectiveness in *DPYD* c.1236G>A (HapB3) carriers receiving fluoropyrimidine dosing reduced by 25%. In the same individual group, significantly increased toxicity was observed. No changes to the dosing recommendation for this risk variant were made based on this publication. Guideline authors stated that particular emphasis should be placed on dose titration after the initial dosing in this individual group.

International Association of Therapeutic Drug Monitoring and Clinical Toxicology

In 2019, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology published recommendations for therapeutic drug monitoring of 5-fluorouracil therapy.[41] The work was supported in part by grants from the National Institutes of Health National Cancer Institute. Several authors reported relationships with Saladax, the manufacturer of the My5-FU assay available in Europe. The committee concluded that there was sufficient evidence to strongly recommend therapeutic drug monitoring for the management of 5-fluorouracil therapy in individuals with early or advanced colorectal cancer and individuals with squamous cell carcinoma of head-and-neck cancer receiving common 5-fluorouracil dosing regimens.

National Comprehensive Cancer Network Guidelines

National Comprehensive Cancer Network (NCCN) guidelines do not recommend use of area under the curve guidance for 5-fluorouracil dosing or genetic testing for *TYMS* variants in individuals with colon,[1] rectal,[42] breast,[43] gastric,[44] pancreatic,[45] or head and neck cancers.[46].

The NCCN Biomarker Compendium provides a grade 2A recommendation for testing for *DPYD* variants prior to use of fluoropyrimidine therapy for the following cancers: ampullary adenocarcinoma, anal carcinoma, appendiceal neoplasms and cancers, breast cancer - invasive breast cancer, cervical cancer, colon cancer, esophageal and esophagogastric junction cancers, gastric cancer, head and neck cancers (including cancer of the nasopharynx), occult primary, penile cancer, rectal cancer, small bowel adenocarcinoma.[47]

Among the NCCN disease-specific guidelines, the guidelines for colon and rectal cancers provide the most detailed discussion of *DPYD* testing and its clinical implications for fluoropyrimidine therapy, stating:[48]

- "FDA added a Black Box warning, recommending to test individuals for genetic variants of *DPYD* prior to initiating capecitabine or fluorouracil unless immediate treatment is necessary. Furthermore, use should be avoided in individuals with certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency. However, no specific test is recommended and there are insufficient data to inform dose adjustments for many of the *DPYD* variants."
- "The NCCN Panel endorses the principle of identifying the patients at the greatest risk for severe fluoropyrimidine toxicity. Testing for *DPYD* genetic variants should be discussed with patients prior to fluoropyrimidine therapy and should be considered in the context of the patient's circumstances."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2012	New policy	
June 2013	Replace policy	Policy updated with literature review, Reference 18 added. No change to policy statement.
June 2014	Replace policy	Policy updated with literature review; references 2, 4-7, 12, 15-16, 30-44 added; others updated and reordered. Investigational OnDose policy statement modified to reflect new test name, My5-FU,. Investigational policy statement for TheraGuide testing for genetic mutations in DPYD or TYMS added. Title changed to reflect information of new test.
June 2018	Replace policy	Policy updated with literature review through January 25, 2018; references 7, 22-23, 25, 27, 29-30, 36, 39-43, 47, and 52 added. "TheraGuide€š removed from policy statement because this test is no longer commercially available; policy statements otherwise unchanged. Title changed to "Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer€š.
June 2019	Replace policy	Policy updated with literature review through January 9, 2019; no references added. Policy statements unchanged.
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through January 22, 2020; references added. Policy statements unchanged.

Date	Action	Description
June 2021	Replace policy	Policy updated with literature review through February 2, 2021; reference added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through January 24, 2022; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through January 31, 2023; references added. "My 5-fluorouracil€š" removed from policy statement because this test is no longer commercially available in the U.S. Minor editorial refinements to policy statements; intent unchanged.
June 2024	Replace policy	Policy updated with literature review through January 12, 2024; reference added. Policy statements unchanged.
June 2025	Replace policy	Policy updated with literature review through January 21, 2025; no references added. Policy statements unchanged.
June 2026	Replace policy	Policy updated with literature review through January 15, 2026; references added. FDA approved language in the prescribing labels was added to the Regulatory Status section and forms the basis of medically necessary policy statements. Existing review of evidence for DPYD testing was not deleted. Medically necessary policy statement on DPYD testing was added; other policy statements unchanged. Title changed to €œLaboratory and Genetic Testing for Use of Fluoropyrimidine Therapy in Individuals With Cancer€□.