



FEP Medical Policy Manual

FEP 2.04.68 Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Effective Policy Date: July 1, 2022

Original Policy Date: December 2012

Related Policies:

None

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

Description

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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 5-fluorouracil dosing and/or treatment in patients with cancer.

POLICY STATEMENT

My 5-fluorouracil™ assay testing or other types of assays for determining 5-fluorouracil area under the curve in order to adjust 5-fluorouracil dose for colorectal cancer patients or other cancer patients is considered **investigational**.

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

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). 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.

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 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 (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 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-fluorouracil is indicated who receive genetic testing for variants (eg, 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 Technology Evaluation Center (TEC) Assessment (2010) concluded that dihydropyrimidine reductase (*DPYD*) and thymidylate synthase (*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 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 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.

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 *DPYD* and/or *TYMS* variants in patients with colon³², rectal,³³ breast,³⁴ gastric,³⁵ pancreatic cancer,³⁶ or head and neck cancers.³⁷

The colon cancer guideline discusses the use of genetic testing for *DPYD* and the risk of severe toxicity after a standard dose of a fluoropyrimidine. Although the guideline discusses evidence for genetic testing for *DPYD*, it states: "However, because fluoropyrimidines are a pillar of therapy in colorectal cancer (CRC) and it is not known with certainty that given *DPYD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time."

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.³⁸ The work was supported in part by grants from the National Cancer Institute National Institutes of Health. Several authors reported relationships with Saladax, the manufacturer of the My5-fluorouracil test. The committee concluded that there was sufficient evidence to strongly recommend therapeutic drug monitoring for the management of 5-fluorouracil therapy in patients with early or advanced colorectal cancer and patients with squamous cell carcinoma of head-and-neck cancer receiving common 5-fluorouracil dosing regimens.

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.¹⁷ 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.190511G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-fluorouracil toxicity. 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 patients 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 patient'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.

National Institute for Health and Care Excellence

In 2014, the NICE published evidence-based diagnostics guidance on the 5-fluorouracil assay for 5-fluorouracil chemotherapy dose adjustment.⁴⁰ The evidence for the guidance was reviewed in February 2018. The guidance stated: "The My5-fluorouracil assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-fluorouracil assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice."

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.

REFERENCES

1. Saladax Biomedical Inc. My5-FU: 5-Fluorouracil (My5-FUTM) Assay. 2022. <https://mycaretests.com/oncology/products/>. Accessed January 24, 2022.
2. Kline CL, Schiccitano A, Zhu J, et al. Personalized dosing via pharmacokinetic monitoring of 5-fluorouracil might reduce toxicity in early- or late-stage colorectal cancer patients treated with infusional 5-fluorouracil-based chemotherapy regimens. *Clin Colorectal Cancer*. Jun 2014; 13(2): 119-26. PMID 24461492
3. Saam J, Critchfield GC, Hamilton SA, et al. Body surface area-based dosing of 5-fluorouracil results in extensive interindividual variability in 5-fluorouracil exposure in colorectal cancer patients on FOLFOX regimens. *Clin Colorectal Cancer*. Sep 2011; 10(3): 203-6. PMID 21855044
4. Gamelin E, Delva R, Jacob J, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *J Clin Oncol*. May 01 2008; 26(13): 2099-105. PMID 18445839
5. Fety R, Rolland F, Barberi-Heyob M, et al. Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clin Cancer Res*. Sep 1998; 4(9): 2039-45. PMID 9748117
6. Yang R, Zhang Y, Zhou H, et al. Individual 5-Fluorouracil Dose Adjustment via Pharmacokinetic Monitoring Versus Conventional Body-Area-Surface Method: A Meta-Analysis. *Ther Drug Monit*. Feb 2016; 38(1): 79-86. PMID 26309030
7. Deng R, Shi L, Zhu W, et al. Pharmacokinetics-based Dose Management of 5-Fluorouracil Clinical Research in Advanced Colorectal Cancer Treatment. *Mini Rev Med Chem*. 2020; 20(2): 161-167. PMID 31660826
8. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. Jul 01 2009; 27(19): 3109-16. PMID 19451431
9. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. Aug 2000; 18(16): 2938-47. PMID 10944126
10. Gamelin E, Boisdron-Celle M, Delva R, et al. Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: results of a multicentric prospective trial of fluorouracil dosage optimization by pharmacokinetic monitoring in 152 patients. *J Clin Oncol*. Apr 1998; 16(4): 1470-8. PMID 9552054
11. Boisdron-Celle M, Craipeau C, Brienza S, et al. Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemother Pharmacol*. Mar 2002; 49(3): 235-43. PMID 11935216
12. Wilhelm M, Mueller L, Miller MC, et al. Prospective, Multicenter Study of 5-Fluorouracil Therapeutic Drug Monitoring in Metastatic Colorectal Cancer Treated in Routine Clinical Practice. *Clin Colorectal Cancer*. Dec 2016; 15(4): 381-388. PMID 27256667
13. Milano G, Etienne MC, Renee N, et al. Relationship between fluorouracil systemic exposure and tumor response and patient survival. *J Clin Oncol*. Jun 1994; 12(6): 1291-5. PMID 8201391
14. Santini J, Milano G, Thyss A, et al. 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. *Br J Cancer*. Feb 1989; 59(2): 287-90. PMID 2930694
15. Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, et al. Relationship between 5-fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. *Cancer*. Feb 01 1996; 77(3): 441-51. PMID 8630950
16. Grem JL. 5-Fluorouracil and its biomodulation in the management of colorectal cancer. In: Saltz LB, ed. *Colorectal Cancer: Multimodality Management*. Totowa, NJ: Humana Press; 2002.
17. Caudle KE, Thorn CF, Klein TE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clin Pharmacol Ther*. Dec 2013; 94(6): 640-5. PMID 23988873
18. ARUP Laboratories. 5-Fluorouracil Toxicity and Chemotherapeutic Response Panel. 2016; <http://tld.aruplab.com/Tests/Pdf/128>. Accessed January 24, 2022.
19. Li Q, Liu Y, Zhang HM, et al. Influence of DPYD Genetic Polymorphisms on 5-Fluorouracil Toxicities in Patients with Colorectal Cancer: A Meta-Analysis. *Gastroenterol Res Pract*. 2014; 2014: 827989. PMID 25614737
20. Rosmarin D, Palles C, Church D, et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. *J Clin Oncol*. Apr 01 2014; 32(10): 1031-9. PMID 24590654
21. Schwab M, Zanger UM, Marx C, et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group. *J Clin Oncol*. May 01 2008; 26(13): 2131-8. PMID 18299612
22. Boige V, Vincent M, Alexandre P, et al. DPYD Genotyping to Predict Adverse Events Following Treatment With Fluorouracil-Based Adjuvant Chemotherapy in Patients With Stage III Colon Cancer: A Secondary Analysis of the PETACC-8 Randomized Clinical Trial. *JAMA Oncol*. May

- 01 2016; 2(5): 655-662. PMID 26794347
23. Vazquez C, Orlova M, Angriman F, et al. Prediction of severe toxicity in adult patients under treatment with 5-fluorouracil: a prospective cohort study. *Anticancer Drugs*. Oct 2017; 28(9): 1039-1046. PMID 28723867
 24. Wang YC, Xue HP, Wang ZH, et al. An integrated analysis of the association between Ts gene polymorphisms and clinical outcome in gastric and colorectal cancer patients treated with 5-FU-based regimens. *Mol Biol Rep*. Jul 2013; 40(7): 4637-44. PMID 23645036
 25. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer. *TEC Assessments*. 2010;24:Tab 13.
 26. Deenen MJ, Meulendijks D, Cats A, et al. Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. *J Clin Oncol*. Jan 20 2016; 34(3): 227-34. PMID 26573078
 27. Henricks LM, van Merendonk LN, Meulendijks D, et al. Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *Int J Cancer*. May 01 2019; 144(9): 2347-2354. PMID 30485432
 28. Henricks LM, Lunenburg CATC, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol*. Nov 2018; 19(11): 1459-1467. PMID 30348537
 29. Goff LW, Thakkar N, Du L, et al. Thymidylate synthase genotype-directed chemotherapy for patients with gastric and gastroesophageal junction cancers. *PLoS One*. 2014; 9(9): e107424. PMID 25232828
 30. Magnani E, Farnetti E, Nicoli D, et al. Fluoropyrimidine toxicity in patients with dihydropyrimidine dehydrogenase splice site variant: the need for further revision of dose and schedule. *Intern Emerg Med*. Aug 2013; 8(5): 417-23. PMID 23585145
 31. Cremolini C, Del Re M, Antoniotti C, et al. DPYD and UGT1A1 genotyping to predict adverse events during first-line FOLFIRI or FOLFOXIRI plus bevacizumab in metastatic colorectal cancer. *Oncotarget*. Jan 30 2018; 9(8): 7859-7866. PMID 29487697
 32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 3.2021. http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed February 2, 2022.
 33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 2.2021. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed February 6, 2022.
 34. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2022. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed February 1, 2022.
 35. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 2.2022. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed February 3, 2022.
 36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2.2021. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed February 5, 2022.
 37. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancer. Version 1.2022. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed February 4, 2022.
 38. Beumer JH, Chu E, Allegra C, et al. Therapeutic Drug Monitoring in Oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology Recommendations for 5-Fluorouracil Therapy. *Clin Pharmacol Ther*. Mar 2019; 105(3): 598-613. PMID 29923599
 39. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther*. Feb 2018; 103(2): 210-216. PMID 29152729
 40. National Institute for Health and Care Excellence (NICE). Fluorouracil chemotherapy: The My5-FU assay for guiding dose adjustment [DG16]. 2014; <https://www.nice.org.uk/guidance/dg16>. Accessed January 24, 2022.

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€□ 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€□.
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.
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.

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