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Therapeutic Drug Monitoring for 5-Fluorouracil

Policy Number: AHS – M2067 – Therapeutic Drug Monitoring for 5-Fluorouracil	Original Effective Date: 06/01/2025 Current Effective Date: 05/01/2026

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I. Policy Description

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.[1]

II. Related Policies

Policy Number	Policy Title
N/A	Not Applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals who are undergoing 5-fluorouracil chemotherapy, therapeutic drug monitoring (TDM) to aid in managing dose adjustment **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2) To aid in managing dose adjustment for individuals undergoing 5-fluorouracil chemotherapy, the following tests **DO NOT MEET COVERAGE CRITERIA**:
   a) Uracil breath tests.
   b) Dihydrouracil/uracil ratio testing of plasma, serum, or urine samples.

IV. Table of Terminology

Term	Definition
5-FU	5-fluorouracil

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AUC	Area-under-curve
BSA	Body surface area
CCyR	Complete cytogenetic response
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRC	Colorectal cancer
CrCl	Creatinine clearance
DPD/DPYD	Dihydropyrimidine dehydrogenase
EMA	European Medicines Agency
FDA	Food and Drug Administration
FP	Fluoropyrimidine
FU	Fluorouracil
GFR	Glomerular filtration rate
GPCO	Groupe de Pharmacologie Cinique Oncologique
HPLC	High-Performance Liquid Chromatography
IATDMCT	International Association of Therapeutic Drug Monitoring and Clinical Toxicology
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LCDs	Local Coverage Determinations
LDT	Laboratory-developed tests
ffpMMR	Major molecular response
NCCN	National Comprehensive Cancer Network
NCDs	National Coverage Determinations
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PK	Pharmacokinetic
PKG	Pharmacokinetically guided
PRAC	Pharmacovigilance risk assessment committee
RCT	Randomized control trials
RNPGx	Francophone Network of Pharmacogenetics
SCCHYN	Squamous cell carcinoma of the head and neck
SFPT	Group of The French Society of Pharmacology and Therapeutics
STP-PT	Therapeutic Pharmacological Monitoring and Personalization of Treatments
TDM	Therapeutic drug monitoring
TOPS	Tyrosine kinase inhibitor optimization and selectivity
TYMS	Thymidylate synthase

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V. Scientific Background

Chemotherapeutic agents encompass a wide variety of medications used to treat cancer. However, due to their cytotoxicity, these agents often have debilitating side effects such as nausea, vomiting, and more. Therefore, it can be useful to identify an "optimal" dose of these agents (for an individual patient) maximize therapeutic efficacy and minimize harmful side effects. Numerous methods to identify an individual's optimal dose exist, such as body surface area (BSA)-based dosing, weight-based dosing, fixed-dose medications, and area-under-curve (AUC) dosing, which is generated by a curve of plasma concentration as a function of time. With both variables known, it would be possible to identify the exact amount of drug exposed to an individual instead of relying on clinical symptoms. AUC-based dosing is typically used for drugs cleared through glomerular filtration (such as carboplatin). However, AUC-based dosing is not usually applicable to most other anticancer agents as elimination of other drugs often involves several other pathways, thereby introducing additional variables that influence drug clearance.[1]

One common therapeutic agent is 5-fluorouracil, or 5-FU. Currently, 5-FU is administered intravenously as a continuous infusion; BSA-based dosage is often used to optimize treatment, and an AUC between 20 and 30 [mg×h×L] is recommended.[2] This particular chemotherapeutic agent can be used alone, or in a combinatory setting, to treat many types of cancer including breast, anal, stomach, colon, head, neck, and some skin cancers.[3] Therapeutic drug monitoring (TDM), known as "the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens,"[4] has shown promise in 5-FU based treatment regimens. In particular, the TDM practice has resulted in reduced toxicity and improved efficacy for the intravenous administration of 5-FU.[5]

Proprietary Testing

Proprietary tests have been developed for identification of the optimal dose of several chemotherapeutic agents. Saladax Biomedical, under the product umbrella termed MyCare, offers a series of tests that aim to find the optimal dose for various chemotherapeutic agents. Their current catalog includes tests for 5-FU (My5-FU), paclitaxel (MyPaclitaxel), docetaxel (MyDocetaxel), and imatinib (MyImatinib). MyCare states that these tests will be able to guide dosing for these agents and minimize toxicity with only a blood test.[6,7] The test is intended for patients receiving 5-FU chemotherapy through intravenous infusion. The test takes plasma near the end of the infusion cycle and is based on the scattered light principle. The amount of scattered light varies inversely with the amount of 5-FU present in the plasma sample. The limit of detection is estimated at 52 ng/mL and the limit of quantitation is estimated at 85 ng/mL. A validated dose adjustment algorithm incorporates the measurements of 5-FU in plasma and uses AUC to calculate subsequent doses.[8]

Additional tests have been proposed to aid in dosing and measuring toxicity in individuals undergoing chemotherapy. Since the efficacy of 5-FU depends on the enzyme dihydropyrimidine dehydrogenase (DPD), the concentration of uracil has been proposed to evaluate pyrimidine, including 5-FU, catabolism. The uracil breath test measures the concentration of carbon dioxide, a pyrimidine metabolic product, after an individual has ingested radiolabeled uracil.[9,10]

Analytical Validity

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Buchel, et al. (2013) compared My5-FU to other commonly used clinical analyzers (Olympus AU400, Roche Cobas c6000, and Thermo Fisher CDx90). A total of 247 plasma samples were measured. The Cobas Integra 800 was found to have a "proportional bias of 7% towards higher values measured with the My5-FU assay" compared to liquid chromatography-tandem mass spectrometry (LC-MS/MS). However, when Cobas Integra 800 was compared to the other three clinical analyzers, only a proportional bias of ≤1.6% and a constant bias below the limit of detection was observed.[11]

Clinical Utility and Validity

Yang, et al. (2016) conducted a meta-analysis of data from two randomized control trials (RCTs) and three 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 found to be associated with "significant improvement in overall response rate (odds ratio = 2.04) 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."[12]

Fang, et al. (2016) performed a meta-analysis to compare the BSA-based algorithm to a pharmacokinetic (PKG)-based algorithm for 5-fluorouracil (5-FU). Four studies (n = 504) were included. The authors found that the PKG algorithm "significantly" improved the objective response rate of 5-FU chemotherapy compared to the BSA-based algorithm. PKG was also found to "markedly" decrease the risk of grade 3/4 adverse drug reactions.[13] Likewise, another study comparing 5-FU TDM to BSA-guided dosing results in patients with gastrointestinal cancer (n = 155) also reports greater interpersonal variability when using a BSA-guided strategy as compared to TDM.[14] A third study demonstrates that TDM can result in even greater improvements in elderly gastrointestinal cancer patients (older than 75 years old) as compared to younger patients (71% improvement in AUC vs. 50% improvement, respectively). This is significant considering that the majority of previous clinical trials excluded elderly patients.[15]

Wilhelm, et al. (2016) evaluated the use of TDM to personalize 5-FU dosing in patients with colorectal cancer. Seventy-five patients were included. The authors aimed to achieve a target AUC of 20-30 mg x h/L and adjusted each cycle of 5-FU accordingly. The average AUC of 5-FU on the initial administration was "18 ± 6 mg × h/L, with 64%, 33%, and 3% of the patients below, within, or above the target AUC range, respectively." By the fourth administration, the average 5-FU AUC was 25 ± 7 mg × h/L, with 54% of patients within the target 5-FU AUC range. The incidence of 5-FU related side effects was reduced compared to historical data despite the increased dose. The authors concluded that "personalization of 5-FU dosing using TDM in routine clinical practice resulted in significantly improved 5-FU exposure and suggested a lower incidence of 5-FU-related toxicities."[16]

Gamelin, et al. (2008) conducted a study to compare conventional dosing of fluorouracil (FU) with pharmacokinetically guided FU dose adjustment in terms of response, tolerability, and survival. A total of 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."[17]

Engels, et al. (2011) examined the effect of pharmacokinetic (PK)-guided docetaxel dosing on interindividual variability in exposure. AUC was used to guide dosing, and 15 patients were included. The authors found that variability (standard deviation) decreased by 35% after one course of PK-guided dosing. However, the authors stated further research was needed.[18]

Joerger, et al. (2007) built a pharmacokinetic-pharmacodynamic model of paclitaxel/carboplatin in ovarian cancer patients. Time above paclitaxel plasma concentration of 0.05 to 0.2 µmol/L (t_c> 0.05−0.2 µmol/L) is thought to be a good predictive marker for severe neutropenia and overall clinical outcome. A total of 139 patients were included in the study; each participant was given "175 mg/m2 over 3 hours followed by carboplatin area under the concentration-time curve 5 mg/mL*min over 30 min." In 34 patients with measurable disease, objective response rate was 76%. Paclitaxel t_c > 0.05 µmol/L was found to be significantly higher in patients with a complete (t = 91.8 hours) or partial response (t = 76.3) compared to patients with progressive disease (t = 31.5). Paclitaxel t_c was also found to predict severe neutropenia well.[19]

A 2017 study by Moeung, et al. (2017) evaluated the efficacy of TDM in patients (n = 89) with advanced germ cell tumors who receive high dose chemotherapy (TI-CE) as compared to using a formula-based covariate equation dosing method. The metric used to assess the efficacy of these two approaches was AUC for carboplatin. TDM was used on 58 of the patients for three days "to develop a covariate equation for carboplatin clearance prediction adapted for future TI-CE patients, and its performance was prospectively evaluated on the other 29 patients along with different methods of carboplatin clearance prediction." Using the developed covariate equation to determine dosing, the researchers showed that the mean AUC was 24.4 mg.min/ml per cycle with 10th and 90th percentiles of 22.4 and 26.8, respectively. They conclude, "TDM allows controlling and reaching the target AUC." An alternative is using "the new equation of carboplatin clearance prediction," a strategy better adapted for young individual patients when TDM cannot be used.[20] However, more recent studies have also shown that the method to determine carboplatin clearance (for example, glomerular filtration rate (GFR) versus estimated creatinine clearance (CrCl)) can have a significant effect on determining the actual AUC for carboplatin.[21]

Guilhot, et al. (2012) evaluated the correlation between "imatinib trough plasma concentrations (C_{min}) and clinical response and safety in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase in the Tyrosine Kinase Inhibitor OPtimization and Selectivity (TOPS) trial." Patients were randomized to 400 mg/day or 800 mg/day of imatinib. The authors found that the C_{min} was stable for patients in the 400 mg/day cohort but showed a slight decrease in the 800 mg/day cohort due to dose adjustments. The rates of major molecular response (MMR) and complete cytogenetic response (CCyR) was found to be significantly lower in patients under the twenty fifth percentile of C_{min} (1165 ng/mL). The authors also observed an association between high imatinib C_{min} and side effects such as edema.[22]

Freeman, et al. (2015) evaluated the clinical and cost effectiveness of the My5-FU assay. The authors compared the assay to gold standards of serum testing and chemotherapeutic dosing. Thirty-five studies regarding clinical effectiveness and 54 studies regarding cost effectiveness were identified. The investigators identified a high "apparent" correlation between My5-FU, high-performance liquid

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chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS), although upper and lower limits of agreement ranged from -18% and 30%. Median overall survival (OS) was found to be 19.6 months for pharmacokinetic dosing (PK) compared to 14.6 months for body surface area (BSA)-guided dosing of 5-FU plus folinic acid. The authors also built a cost-effectiveness model for the My5-FU assay for metastatic colorectal cancer and head and neck cancer. The model showed My5-FU to be 100% cost effective at £20,000 per quality-adjusted life-year for both types, although the head and neck cancer was only an estimate. Despite these findings, the authors noted that "considerable uncertainties remain about evidence quality and practical implementation."[23]

Cunha-Junior, et al. (2013) studied the use of the uracil breath test to determine 5-FU toxicity in gastrointestinal cancer patients (n = 33). Their results show that the uracil breath test had a sensitivity and specificity of 61.5% and 85%, respectively in distinguishing individuals with grade 3-4 versus grade 0-1 toxicity. Likewise, the sensitivity and specificity of distinguishing DPD-deficiency versus non-DPD-deficiency are 75% and 85%, respectively. The authors conclude that the uracil breath test "has moderate accuracy in discriminating individuals who manifested severe toxicity from those who had mild or no toxicity to 5FU."[9]

Lee, et al. (2016) reviewed the critical role of therapeutic drug monitoring (TDM) in optimizing 5-fluorouracil (5-FU) therapy. Through identifying key publications, the author noted that "pharmacokinetic studies of 5-FU systemic exposure have shown a wide range of interpatient variation of 5-FU plasma drug level."[24] Such variability contributes to underexposure, reducing antitumor efficacy, or overexposure, leading to severe toxicities such as "febrile neutropenia, nausea/vomiting, and diarrhea."[24] The author also emphasized that, given 5-FU's "extremely short half-life and cell cycle-specific cytotoxic effects,"[24] continuous infusion combined with TDM has been refined over four decades into a validated algorithm that allows reliable dose adjustment based on plasma level.

Macaire, et al. (2019) researched the effects of TDM to optimize 5-FU chemotherapy in gastrointestinal cancer patients under and over 75 years of age. A total of 154 participants with gastrointestinal cancer participated in this study; thirty-one participants were older than 75 years of age. "At cycle 1 (C1), the 5-FU dose was calculated using patient's body surface area, then a blood sample was drawn to measure 5-FU concentration and 5-FU dose was adjusted at the subsequent cycles based on C1 concentration. Assessments of toxicity were performed at the beginning of every cycle."[15] Results show that approximately 71% of patients older than 75 years of age required dose adjustments after C1, while only 50% of younger patients required adjustments. Further, after dose adjustments, by cycle 3 (C3), the percentage of patients above age 75 with severe 5-FU related toxicity fell from 15% to 5%. The authors conclude that "Pharmacokinetic-guided 5-FU-dosing algorithm, leading to an improved tolerability while remaining within therapeutic concentration range, is even more valuable for patients older than 75 years than in younger patients."[15]

Deng, et al. (2020) studied the efficacy of pharmacokinetic-based 5-FU dosing management in advanced colorectal cancer patients. A total of 153 patients with advanced colorectal cancer were randomized to receive a double-week chemotherapy with 5-FU using pharmacokinetic dosing or 5-FU chemotherapy with BSA guided dosing. In the first four weeks of treatment, patients in the experimental group were administered 5-FU according to the classic strategy of body surface area dosing before transitioning into pharmacokinetic AUC-based dosing. For the duration of the study, all patients in the control group continued with BSA guided chemotherapy. The efficacy, toxic side effects, and survival rate were assessed throughout the study. In the AUC-based dosing (experimental) group, "the rate of diarrhea

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significantly decreased (37.50% vs. 70.00%, P=0.010), and incidence of oral mucositis reduced (54.17% vs. 82.50%, P=0.014). Compared with the control group, the clinical benefit rate of experimental group was much higher (90.79% vs. 79.22%, P=0.046)." There was no significant difference in other 5-FU related toxic side effects such as nausea or vomiting and no difference in progression-free survival between the two groups. The authors concluded that "pharmacokinetic- based dose management of 5-Fluorouracil reduces the toxicity of chemotherapy and improves long-term efficacy of chemotherapy for advanced colorectal cancer patients."[25]

Dolat, et al. (2020) studied how evaluating DPD deficiency before initiating 5-FU treatment could help limit 5-FU toxicity by investigating the relationship between 5-GU clearance and DPD activity markers. There were 169 patients with colorectal, pancreas, and metastatic cancer included in the study and the DPD marker, uracilemia (U), was measured. Overall, all patients benefited from a pre-therapeutic DPYD genotyping and phenotyping. There was no correlation between uracilemia levels and 5-FU clearance. However, in patients with low DPD marker levels (U<16 ng/mL), 5-FU exposure was higher than in other patients and these patients benefited from an increase in dose following 5-FU therapeutic drug monitoring (TDM). The author states that if guidelines recommend decreasing the 5-FU dose in patients with U > 16 ng/mL, then these patients are at risk of under-exposure and 5-FU TDM should be conducted to avoid loss of efficacy.[26]

Vithanachchi, et al. (2021) reviewed the economic evaluations of TDM interventions for certain cancer drugs. Through identifying 11 publications, the researchers found that TDM with imatinib and TDM with 5-FU were the “most commonly assessed interventions.” Using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist, they evaluated the quality of reporting of economic evaluations, and found that these publications met 61-91% of CHEERS checklist criteria. Additionally, “all publications considered TDM to be cost-effective based on an incremental cost-effectiveness ratio below the willingness to pay threshold (64%) or being cost-saving (36%),” and TDM interventions were likely to be “cost-effective in an oncology landscape where treatments offering small benefits have high cost.” To fully evaluate the impact of TDM, the researchers also suggest assessing uncertainties in the clinical evidence for newer treatments used alongside or after TDM treatment. This research elucidated the context by which TDM could be beneficial fiscally and how that may impact future care.

Laures, et al. (2022) investigated DPD deficiency screening using uracil-based phenotyping to see whether it reduced the negative side effects of 5-Fluorouracil-based chemotherapy. French recommendations call for screening for DPD deficiency (through plasma uracil quantification) before instituting fluoropyrimidine-based chemotherapy. A total of 198 patients who received 5-FU therapy (these participants had DPD deficiency) were compared to 94 reference patients. According to the authors, the study showed a reduction in 5-FU serious toxic events during the first four courses of chemotherapy. Their analysis “identified a significant difference in adverse effects toxicity coupled with their frequency between patients with an identified DPD phenotype and patients with an unknown DPD phenotype.” However, the authors also described how various studies of DPD deficiency have given conflicting results. For example, a separate study “demonstrated no significant difference in the prevalence of toxicities between DPD-deficient and non-deficient patients, suggesting that further work is needed to investigate the association of phenotyping with toxicity.”[28,29]

In the PREDICT-5FU trial, Glewis, et al. (2025) studied 5-fluorouracil (5-FU) exposure in a diverse cancer cohort receiving standard regimens and evaluated the feasibility of implementing 5-FU and capecitabine therapeutic drug monitoring (TDM) in clinical practice. A total of 50 patients with a median age of 63

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years were recruited. All patients underwent pharmacogenetic testing, and serial plasma sampling was used to calculate drug exposure (AUC). Results showed that "only 36% of 5FU patients achieved target AUC when dosed based on body surface area; 61% were below and 3% above target range."[30] However, the author concluded that after "post TDM-adjusted dosing, target AUC was achieved in 58% of patients (22% absolute increase vs. BSA dosing, p = 0.03), within median three cycles (range 1–5)."[30] These findings demonstrate that TDM substantially improves the precision of 5-FU dosing, and when combined with pharmacogenetic assessment, provides a more reliable strategy than BSA-based dosing alone to balance efficacy and safety in routine oncology practice.

VI. Guidelines and Recommendations

International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

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."[8,31]

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.[31]

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."[31]

National Comprehensive Cancer Network (NCCN)

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. Docetaxel, 5-FU and paclitaxel are listed as having 10-30% emetic risk whereas imatinib <=400 mg/day is listed as <30% risk. No information regarding therapeutic drug monitoring was included.[32] Furthermore, the NCCN did not address TDM in either its colon cancer or head and neck cancer guidelines.[33,34]

National Institute for Health and Care Excellence (NICE)

The NICE remarked that the My5-FU assay should only be recommended for research purposes, although they noted that it has "promise."[8] In a December 2017 review of the 2014 guideline, NICE stated that no changes were required.[35]

Clinical Pharmacogenetics Implementation Consortium (CPIC)

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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."[36]

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)

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."[37]

Francophone Network of Pharmacogenetics (RNPGx) and the French Clinical Oncopharmacology Group (GPCO)-UNICANCER

Etienne-Grimaldi, et al. (2023) released "Current diagnostic and clinical issues of screening for dihydropyrimidine dehydrogenase deficiency [DPD]," which included recommendations for FP-based chemotherapy. The guideline recommends the following:

- "EMA recommends DPD testing (*DPYD* variants or uracilemia) before FP-based chemotherapy.
- Genotyping relevance of the 4 consensual *DPYD* variants is restricted to Caucasians.
- *DPYD* genotype-guided FP dose reduction is clinically validated, contrary to uracilemia.
- Impact of DPD-guided FP dose reduction on efficacy needs further investigation.
- 5FU therapeutic drug monitoring is recommended in partial DPD-deficient patients."[38]

European Medicines Agency (EMA)

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In 2020, the pharmacovigilance risk assessment committee (PRAC) of EMA published an assessment report on "Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products." The committees recommend the following:

- "To minimise the risk of increased toxicity, PRAC recommended that DPD deficiency testing is conducted before initiation of treatment. PRAC considered genotyping and phenotyping by evaluation of blood uracil levels tests as being currently the most suitable methods to identify patients with DPD deficiency."
- "PRAC confirmed the current knowledge that the use of 5-fluorouracil for systemic use and related substances in patients with DPD deficiency is associated with an increased risk of toxicity."
- "The PRAC concluded that the benefit-risk balance of 5-fluorouracil (i.v.) and related substances capecitabine, tegafur and flucytosine is negative in patients with complete DPD deficiency and confirmed that these medicinal products should be contra-indicated in patients with known complete DPD deficiency. PRAC also concluded that patients with partial DPD deficiency should be treated with an adjusted starting dose."[39]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

The FDA's "Prescribing Information" documents for fluorouracil, paclitaxel, imatinib, and docetaxel do not include AUC as a method to adjust dosage.[40-43]

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
S3722	Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil
80299	Quantitation of therapeutic drug, not elsewhere specified
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
83789	Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

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IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
05/01/2026	Clinical Advisory Board Meeting, policy review and approval: 12/03/2025 Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria.
06/01/2025	Initial Policy Implementation

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