Medical Policy

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***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic and Laboratory Testing for Use of 5-Fluorouracil in Patients with Cancer

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Description/Background

Variability in systemic exposure to 5-fluorouracil (5-FU) chemotherapy is thought to directly impact 5-FU tolerability and efficacy. The standard approach is dosing according to body surface area (BSA). Two alternative approaches have been proposed for modifying use of 5-FU: (1) dosing based on the determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-FU 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-FU metabolism, respectively.

5-FLUOROURACIL
The agent 5-fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets the thymidylate synthase (TYMS) enzyme, which is involved in DNA production.(1) 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 III or IV 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 the 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.(2,3) 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 Act (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. (The LDT TheraGuide® by Myriad Genetics has been discontinued). 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.

Medical Policy Statement

The clinical utility of laboratory assays, including My5-FU™, for determining 5-fluorouracil (5-FU) area under the curve (AUC) in order to adjust 5-FU dosing for cancer patients has not been demonstrated. The peer reviewed medical literature has not shown that these tests significantly improve patient outcomes. Therefore, this service is experimental/investigational.

The clinical utility of genetic tests for mutations in dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) to guide 5-FU dosing and/or to select treatment in patients with cancer has not been demonstrated. The peer reviewed medical literature has not shown that these tests significantly improve patient outcomes. Therefore, this service is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81232 81346 S3722

Rationale

LABORATORY TESTING TO DETERMINE 5-FLUOROURACIL AREA UNDER THE CURVE FOR DOSE ADJUSTMENT

Clinical Context and Test Purpose

The purpose of laboratory testing is to use test results to guide 5-fluorouracil (5-FU) dosing so that the therapeutic impact is maximized and the toxicity is decreased.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest is patients with cancer who have an indication for 5-FU treatment.

Interventions

The test being considered is laboratory assays to determine 5-FU area under the curve (AUC).

Patient exposure to 5-fluorouracil is most accurately described by estimating the area under the curve, the total drug exposure over a defined period of time. 5-fluorouracil exposure is influenced by the method of administration, circadian variation, liver function, and the presence of inherited dihydropyrimidine reductase (DPYD)-inactivating genetic variants that can greatly reduce or abolish 5-fluorouracil catabolism. As a result, both inter- and intrapatient variability in 5-fluorouracil plasma concentration during administration is high.

Determination of 5-fluorouracil area under the curve requires complex technology and expertise that may not be readily available in a clinical laboratory setting.

The association between area under the curve-monitored (My5-fluorouracil) versus body surface area (BSA) dosing strategies has been examined in colorectal cancer patients who received 5-fluorouracil regimens.(4,5)

Comparators

The following practice is currently being used to make decisions about dosing of 5-FU: Standard BSA-dosing.

Body surface area-based dosing is associated with wide variability in pharmacokinetic parameters leading to significant differences in individual exposure. Nevertheless, body surface area-based dosing is the standard for most chemotherapeutic agents.

Outcomes

There is a relatively narrow therapeutic window for 5-fluorouracil and levels of exposure leading to toxicity and efficacy overlap. Therefore, both safety and efficacy outcomes are of interest in evaluating evidence.

The general outcomes of interest related to 5-FU toxicity are types of severe toxicity such as cardiotoxicity, neutropenia, diarrhea, mucositis, and hand-foot syndrome.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs).
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse effects, single-arm studies were sought that capture longer periods of follow-up and/or larger populations.
- Duplicative or studies with overlapping populations were excluded.

Review of Evidence

Meta-Analysis
Yang et al (2016) published a meta-analysis of data from the 2 RCTs described below (Gamelin et al, 2008 [6] and Fety et al, 1998 [7]), as well as from 3 observational studies.(8) In a pooled analysis, the overall response rate was significantly higher with pharmacokinetic AUC-monitored 5-FU therapy than with standard BSA-based monitoring (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.41 to 2.95). In terms of toxicity, incidence of diarrhea (three studies), neutropenia (three studies), and hand-foot syndrome (2 studies) did not differ significantly between the pharmacokinetic and BSA monitoring strategies. The rate of mucositis was significantly lower in the BSA-monitored group (three studies; OR=0.16; 95% CI, 0.04 to 0.63). Most data were from observational studies, which are subject to selection and observational biases.

Randomized Controlled Trials
The best contemporary evidence supporting area under the curve-targeted dosing consists of 32 RCTs, 21 enrolling patients with colorectal cancer and the other enrolling patients with head and neck cancer. No trials of any design were identified for 5-fluorouracil dose adjustment in other malignancies. The characteristics and key results of the RCTs are summarized in Tables 1 and 2.

Deng et al (2020) conducted an RCT in patients with advanced colorectal cancer who were treated with 5-fluorouracil (FOLFOX or FOLFIRI).(9) 5-fluorouracil was dosed using body surface area for all patients in the first period, then patients were randomized to receive area under the curve-guided dosing (adjusted via an algorithm) or BSA-guided dosing for subsequent periods. The percentage of patients in the therapeutic window (area under the curve between 20 to 30 mg/h/L) was 24.52% with BSA dosing. With the area under the curve dosing, the percentage of patients in the therapeutic range was 18.42% in the first period which increased to 89.71% in the sixth (and final) period. In the area under the curve-guided dosing, grade 3 toxicities were reduced and more patients experienced a clinical benefit, defined as partial response or stable disease.

In an RCT enrolling patients with metastatic colorectal cancer, Gamelin et al (1998) reported significantly improved tumor response (33.6% vs 18.3%, respectively; $p<0.001$) and a trend toward improved survival (40.5% vs 29.6%, respectively; $p=0.08$) in the experimental arm using AUC-targeted dosing (by HPLC) for single-agent 5-FU compared to fixed dosing.(6) However, trialists also reported 18% grade 3 to 4 diarrhea in the fixed-dose control arm, higher than reported in comparable arms of 2 other large chemotherapy trials (5%-7%).(10,11) In the latter 2 trials, the delivery over a longer time period for both 5-FU (22 hours vs 8 hours) and leucovorin (2 hours vs bolus), which is characteristic of currently recommended 5-FU treatment regimens, likely minimized toxicity. The administration schedule used in the Gamelin et al (2008) trial (6) is rarely currently used in clinical practice and is absent from available

guidelines.(5) Additional optimization studies would be needed to apply 5-FU exposure monitoring and AUC-targeted dose adjustment to a more standard single-agent 5-FU treatment regimen, with validation in a comparative trial vs a fixed-dose regimen.

Fety et al (1998), in an RCT of patients with locally advanced head and neck cancer, used a different method of dose adjustment and reported overall 5-FU exposures in head and neck cancer patients that were significantly reduced in the dose-adjustment arm compared with the fixed-dose arm.(7) This reduced toxicity but did not improve clinical response. The dose-adjustment method in this trial may have been too complex, because the 12 patients with protocol violations in this treatment arm (of 61 enrolled) all were related to 5-FU dose adjustment miscalculations. Because patients with protocol violations were removed from analysis, results did not reflect “real-world” results of the dose-adjustment method. In addition, the induction therapy regimen used 2 drugs, not the current standard of 3, and, therefore, generalizability of results to current clinical practice is limited.

Table 1. Summary of Key Randomized Trials Characteristics

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Deng et al (2020)	China	1	2015-2016	Patients with advanced CRC intended to be treated with FU-based chemotherapy (N=153)	AUC-based dosing (My 5-FU test)	BSA-guided dosing
Gamelin et al (2008)	France	5	NR	Patients with metastatic CRC intended to be treated with FU-based chemotherapy (N=208)	AUC-based dosing (Test NR)	BSA-guided dosing
Fety et al (1998)	France	NR	NR	Patients with local head and neck carcinomas who were treated with 5-fluorouracil (N=122)	AUC-based dosing (HPLC analysis)	Standard dose (4 g/m^2 per cycle)

5-FU: 5-fluorouracil; AUC: area under the curve; BSA: body surface area; CRC: colorectal cancer; FU: fluoropyrimidine; HPLC: high performance liquid chromatography; NR: not reported.

Table 2. Summary of Key Randomized Trials Results

Study	Toxicity		Overall Response Rate	Median Overall Survival or PFS
Deng et al (2020)	Grade 3 Toxicity		Clinical Benefit Rate (partial response and stable disease)	PFS
Group 1: BSA-guided dosing (n=77)	51.95%		79.22%	11 months
Group 2: AUC-based dosing (n=76)	31.58%		90.79%	16 months
p-value	p=0.010		p=0.046	p=0.115
Gamelin et al (2008)			Overall response rate (complete or partial response)	Overall survival rate
Group 1: BSA-guided dosing (n=96)	NR		18.3%	59.5% (1 year); 29.6% (2 years)
Group 2: AUC-based dosing (n=90)	NR		33.6%	70.5% (1 year); 40.5% (2 years)
p-value	Toxicity was more prevalent with Group 1 vs. Group 2 (overall percentages NR) p=0.003		p=0.0004	p=0.08 (2 years)
Fety et al (1998)	Grade 3-4 Hematologic Toxicity	Grade 3-4 Mucositis	Objective response rate (complete or partial response)	
Group 1: Standard dose (n=57)	17.5%	5.1%	77.2%	NR

Group 2: AUC-based dosing (n=49)	7.6%	0%	81.7%	NR
p-value	p=0.013	p<0.01	p=0.03 for equivalence	

AUC: area under the curve; BSA: body surface area; NR: not reported; PFS: progression free survival

Tables 3 and 4 display notable limitations identified in each study.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Deng et al (2020)	2. Study population is unclear				
Gamelin et al (2008)	2. Study population is unclear				
Fety et al (1998)	2. Study population is unclear	2. Version used unclear	2. Not compared to credible reference standard		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2.Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do notreflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Deng et al (2020)	1. Selection not described	1. Not blinded				2. Comparison to other tests not reported
Gamelin et al (2008)	1. Selection not described	1. Not blinded				2. Comparison to other tests not reported
Fety et al (1998)	1. Selection not described	1. Not blinded	1. Timing of delivery of index or reference test not described		2. High number of samples excluded	2. Comparison to other tests not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Single-Arm Studies

The results of single-arm trials of area under the curve-targeted 5-fluorouracil dose adjustment in advanced colorectal cancer patients have suggested consistently improved tumor response.(12-14) Similar, although less compelling, results were seen in single-arm trials of area under the curve-targeted 5-fluorouracil dosing in head and neck cancer.(15,16) Gamelin et al (1998) developed a chart for weekly dose adjustment based on the results of an earlier,

similar single-arm study (1996)(17) in which dose was increased by prespecified increments and intervals up to a maximum dose or the first signs of toxicity.

Section Summary: Laboratory Testing to Determine 5-fluorouracil Area Under the Curve for Dose Adjustment

Most RCTs and nonrandomized comparative studies comparing health outcomes were either single-center or did not use chemotherapy regimens used in current clinical practice. One recent RCT did find a clinical and safety benefit of use of area under the curve-targeted 5-fluorouracil dosing in patients with colorectal cancer. A systematic review of the available literature found a significantly higher response rate with BSA-based monitoring and no significant difference in toxicity. Most data were from observational studies; several of which were conducted in the 1980s when different chemotherapy protocols were used.

TESTING FOR *DPYD* OR *TYMS* VARIANTS IN AFFECTING 5-FU DOSE ADJUSTMENT

Clinical Context and Test Purpose

The proposed purpose of genetic testing is to use test results to guide 5-FU dosing so that the therapeutic impact is maximized and the toxicity is decreased.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are patients with cancer who have an indication for 5-FU treatment.

Interventions

The test being considered is genetic testing for variants (e.g., in *DPYD* and *TYMS*) affecting 5-FU metabolism.

5-fluorouracil is a pyrimidine antagonist, similar in structure to the normal pyrimidine building blocks of RNA (uracil) and DNA (thymine). More than 80% of administered 5-fluorouracil is inactivated and eliminated via the catabolic pathway; the remainder is metabolized via the anabolic pathway.

Catabolism of 5-fluorouracil is controlled by the activity of DPYD. Because DPYD is a saturable enzyme, the pharmacokinetics of 5-fluorouracil are strongly influenced by the dose and schedule of administration.(18) For example, 5-fluorouracil clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-fluorouracil during the course of therapy. Genetic variants in DPYD, located on chromosome 1, can lead to reduced 5-fluorouracil catabolism and increased toxicity. Many variants have been identified (e.g., IVS14+1G>A [also known as DPYD*2A], 2846A>T [D949V]). DPYD deficiency is an autosomal co-dominantly inherited trait.(19)

The anabolic pathway metabolizes 5-fluorouracil to an active form that inhibits DNA and RNA synthesis by competitive inhibition of TYMS or by incorporation of cytotoxic metabolites into nascent DNA.(20) Genetic variants in TYMS can cause tandem repeats in the TYMS enhancer region (TSER). One variant leads to 3 tandem repeats (TSER*3) and has been associated with 5-fluorouracil resistance due to increased tumor TYMS expression compared with the TSER*2 variant (two tandem repeats) and wild-type forms.

A number of studies have evaluated the association between variants in the DPYD and/or TYMS genes and 5-fluorouraciltoxicity. Cancer types and specific variants studied differed across these reports.(21-26)

Comparators
The following practice is currently being used to make decisions about dosing of 5-FU: standard BSA-based dosing.

Outcomes
There is a relatively narrow therapeutic window for 5-fluorouracil and levels of exposure leading to toxicity and efficacy overlap. The beneficial outcome of a true-positive (identifying a variant that would have caused severe toxicity) is prevention of toxicity. However, the harmful outcome of a false-positive is withholding or premature cessation of effective chemotherapy which may compromise chemotherapy effectiveness.

Therefore, both safety and efficacy outcomes are of interest in evaluating evidence. The outcomes of interest related to 5-FU toxicity are types of severe toxicity such as cardiotoxicity, neutropenia, diarrhea, mucositis, and hand-foot syndrome.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs).
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse effects, single-arm studies were sought that capture longer periods of follow-up and/or larger populations.
- Duplicative or studies with overlapping populations were excluded.

Review of Evidence
A TEC Assessment (2010) concluded that *DPYD* and *TYMS* variant testing did not meet TEC criteria.(27) The Assessment noted that the tests had “poor ability to identify patients likely to experience severe 5-FU toxicity. Although genotyping may identify a small fraction of patients for whom serious toxicity is a moderate to strong risk factor, most patients who develop serious toxicity do not have variants in *DPD* or *TS* genes.”(27)

Nonrandomized Studies
Several recent prospective observational studies have reported safety and effectiveness outcomes in patients who received genetic testing prior to receiving a 5-FU-based chemotherapy regimen. Characteristics and results of these studies are shown in Tables 5 and 6. Three of these, conducted by the same research group in the Netherlands, used historical controls.(28-30) and one also included a matched-pairs analysis using previously collected data.(29) The others were single-arm, uncontrolled studies.(31-33) No prospective trials comparing efficacy and safety outcomes using concurrent control groups with or without pretreatment *DPYD* and/or *TYMS* testing were identified.

Henricks et al (2019) included 3 comparison groups in a prospective cohort study in which patients received genotyping prior to treatment as part of routine care.(29) Group I (n=40) were DPYD*2A carriers treated with an approximately 50% reduced fluoropyrimidine

dose. Group II (n=1606) were wild-type patients who had been identified as part of an earlier study (Deenan et al [2016];(28) discussed below) and treated with a standard dose. Group III (n=86) were DPYD*2A carriers, identified from the literature, treated with a standard dose. Safety outcomes of the first 18 of the 40 patients in Group I were previously reported in Deenan et al (2016).(28) Patients in Group I were matched to those in Group II for the primary analysis for covariables known to influence treatment outcome. The primary effectiveness endpoint was OS. Secondary endpoints were progression-free survival and tumor response. Of the patients included in Groups 1 and 2, 96% of patients were White, 1% of patients were Southeast Asian, 1.3% of patients were African, and 1.7% of patients did not have their ethnicity or race described.

In matched-pair comparisons, Groups I and II did not differ on OS (hazard ratio 0.82; 95% CI 0.47 to 1.43; P=0.47), progression-free survival (hazard ratio 0.83; 95% CI 0.47 to 1.50; p=0.54), or tumor response (0% vs 5% complete response; 20% vs 34% partial response; p>0.99), suggesting that the lower dose did not have a detrimental effect on treatment response in *DPYD*2A* carriers. The incidence of treatment-related toxicity, including overall toxicity, gastrointestinal toxicity, hematological toxicity, and hand-foot syndrome, was higher in the genotype-guided dosing group compared to wild-type patients, but differences were not statistically significant. Compared to the historical literature cohort who had received standard dosing, Group I patients had a lower risk of severe toxicity (77% vs 18%; P<0.001). There were no treatment-related deaths in the genotype-guided group, compared to 7 of 86 (8%) in the historical cohort. This study had several methodological limitations. Although patients were prospectively genotyped, data collection of outcomes was retrospective. A historical control group was used for the assessment of adverse events. There was a relatively large amount of missing data, small sample size, and the study was underpowered. Because it was conducted at a single-institution, its results may not be generalizable to other settings.

Deenan et al (2016) compared outcomes for pretreatment *DPYD*2A* testing with historical controls.(28) The study included cancer patients intending to undergo treatment with fluoropyrimidine-based therapy (5-FU or capecitabine).(28) Genotyping for *DPYD*2A* was performed before treatment, and dosing was adjusted based on the alleles identified. Patients with heterozygous variant alleles were treated with a reduced (i.e., ≥50%) starting dose of fluoropyrimidine for 2 cycles, and dosage was then individualized based on tolerability. No homozygous variant allele carriers were identified. Safety outcomes were compared with historical controls. Twenty-two (1.1%) of 2038 patients were heterozygous for *DPYD*2A*. Eighteen (82%) of these 22 patients were treated with reduced doses of capecitabine. Five (23%; 95% CI, 10% to 53%) patients experienced grade III or higher toxicity. In historical controls with *DPYD*2A* variant alleles, the rate of grade III or higher toxicity was 73% (95% CI, 58% to 85%). The historical controls were more likely to be treated with 5-FU based therapy than with capecitabine-based therapy. Trial limitations included lack of randomization to a management strategy and use of historical, rather than concurrent, controls. Relevant diversity was also not well represented, as 96% of patients were White, 1% of patients were Asian, and 3% of patients did not have their ethnicity or race described.

Henricks et al (2018) conducted a prospective study of adult patients with cancer who were intended to start fluoropyrimidine based therapy.(30) Patients were enrolled from 17 hospitals in the Netherlands. Dose reductions were based on genotyping: Heterozygous DPYD variant allele carriers received an initial dose reduction of either 25% (for c.2846A>T and c.1236G>A) or 50% (for *DPYD*2A* and c.1679T>G). The researchers compared adverse events in the

prospectively genotyped group who received genotype-based dosing, wild-type patients identified through prospective genotyping, and a historical control group of patients from a previously published meta-analysis who were DPYD variant carriers but did not receive genotype-guided dosing. The primary outcome was the frequency of severe treatment-related toxicity. Survival and response were not assessed. There was a higher incidence of grade 3 or higher toxicity in the genotype-dosing group compared to wild-type patients (39% vs 23%; p=0.0013).The relative risk for severe toxicity in DPYD*2A carriers who did not have genotype-guided dosing was 2.87 (95% CI 2.14 to 3.86), compared to 1.31 (0.63 to 2.73) in the cohort that received genotype-based dosing. The main limitation of this study is its use of a historical control group, with no control for confounders in the analysis. Relevant diversity was also not well represented, as 95% of patients were White, 2% of patients were Asian, 2% of patients were Black, and 1% of patients did not have their ethnicity or race described.

Cremolini et al (2018) (33), reported chemotherapy-related adverse events experienced by patients with metastatic colon cancer who were enrolled in the phase III RCT and treated with first-line FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab. Of 508 randomized patients, 443 (87%) were genotyped for *DPYD* and UGT1A1 variants. All patients received study treatments at planned doses; dosage was not adjusted based on genotyping. Overall eight of 10 patients who were *DPYD* carriers experienced grade III or higher adverse events. An advantage of this study was that it used prospectively and systematically collected data on adverse events. It is limited by the lack of a comparison group and because genotype-based dosing was not used.

Goff et al (2014) prospectively genotyped 42 adults who had gastric or gastroesophageal junction cancer for *TSER* tandem repeats.(31) Of the 26 patients included initially in the study, 88% of patients were White, 8% were African American, and 4% did not have their race or ethnicity described. Twenty-five patients who had TSER 2R/2R or 2R/3R genotypes received a modified 5-FU chemotherapy regimen until unacceptable toxicity or disease progression (median, 5.5 cycles); patients homozygous for triplet repeats (3R/3R) were excluded. The overall response rate in 23 evaluable patients was 39% (9 partial responses, no complete responses), which was worse than a 43% historical overall response rate in unselected patients. The overall response rate in 6 patients homozygous for doublet repeats (2R/2R) was 83% (5 partial responses, no complete responses). Median OS and progression-free survival in the entire cohort (secondary outcomes) was 11.3 months and 6.2 months, respectively; these rates were similar to those reported in unselected populations. The study was stopped before meeting target enrollment (minimum 75 patients) due to insufficient funding.

Magnani et al (2013) reported on 180 cancer patients receiving fluoropyrimidines (5-FU or capecitabine) who underwent *DPYD* analysis for the *1905+1* G>A variant by high-pressure liquid chromatography.(32) Four patients were heterozygous carriers. Of these, 3 patients received dose reduction of 50% to 60% but still experienced severe toxicities requiring hospitalization. One patient did not receive chemotherapy based on *DPYD* genotype and the presence of other variants found in mismatch repair genes.

Table 5. Summary of Key Nonrandomized Trials Characteristics

Study	Study Type	Country	Dates	Participants	Treatment
Henricks (2019)	Prospective screening, retrospective data collection, historical control groups	Netherlands	2007-2015	Patients intended to be treated with FU-based chemotherapy (n=1732)	Genotyping for DPYD*2A

Henricks (2018)	Prospective, with historical control	Netherlands	2015-2017	Patients intended to be treated with FU-based chemotherapy (n=1181)	Genotyping for DPYD*2A,
Cremolini (2018)	Prospective, uncontrolled	Italy	2008-2011	Patients with metastatic colorectal cancer who were treated with 5-FU and irinotecan-based chemotherapy in an RCT (n=443)	Genotyping for DPYD*2A
Deenen (2016)	Prospective, with historical control	Netherlands	2007-2011	Patients intended to be treated with FU-based chemotherapy (n=2038)	Genotyping for DPYD*2A
Goff (2014)	Prospective, uncontrolled	US	2008-2010	Adults with gastric or gastroesophageal junction cancer (n=25)	Genotyping for TSER tandem repeats
Magnani (2013)	Prospective, uncontrolled	Italy	2011-2012	Patients diagnosed with gastrointestinal, breast, head and neck, and other tumors (n=180)	DPYD analysis

FU: fluoropyrimidine; RCT: randomized controlled trial. TSER: thymidylate synthase enhancer region.

Table 6. Summary of Key Nonrandomized Trials Results

Study	Heterozygous Carrier Patients	Grade 3 Toxicity	Overall Response Rate	Median Overall Survival
Henricks (2019)				
Group 1: DPYD*2A carriers, reduced dose (n=40)	40	7/40 (18%)	0% complete response, 20% partial response, 40% stable	27 months (range 1-83 months)
Group 2: Wild-type, standard dose (n= 1606)	NA	372/1606 (23%)	5% complete response, 29% partial response, 14% stable	24 months (range 0.7 to 97 months)
Group 3: DPYD*2A carriers, standard dose (n= 86)	86	66/86 (77%)	NR	
Hazard ratio (95% CI)				Group 1 vs Group 2 0.82 (0.47 to 1.43)
p-value		Group 1 vs Group 2: 0.57 Group 1 vs group 3: <0.001	Group 1 vs Group 2: >0.99	Group 1 vs Group 2: 0.47
Henricks (2018)			NR	NR
DPYD*2A carriers, genotype-guided dosing	85/1181 (7.7%)	33/85 (39%) RR 1.31 (95% CI 0.63 to 2.73)		
Historical control (DPYD*2A carriers, standard dose)		RR 2.87 (95% CI 2.14 to 3.86)		
Relative risk (95% CI)				
Historical control (wild-type, standard dosing)		231/1018 (23%); p<0.0013 vs genotype guided dosing cohort	NR	NR
Cremolini (2018)	10/439 (2.2%)	8/10 (80%)	NR	NR
Deenen (2016)	22/2038 (1.1%)	28%	NR	NR
P-value		<0.001		

Goff (2014)	NR	NR	39.1% (9 partial responses, no complete responses)	11.3 months; 6.2 months
95% CI			22.2-59.2	
Magnani (2013)	4 (2.2%)	NR	NR	NR

CI: confidence interval; DPYD: dihydropyrimidine reductase; NA: not applicable; NR: not reported; RR: relative risk

Tables 7 and 8 display notable limitations identified in each study.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Henricks (2019)	4. Enrolled populations do not reflect relevant diversity		historical control group		
Henricks (2018)	4. Enrolled populations do not reflect relevant diversity		historical control group	1. no effectiveness outcomes	
Cremolini (2018)	2. Study population is unclear	3. genotype-based dosing not used	no control group	1. no effectiveness outcomes	
Deenen (2016)	4. Enrolled populations do not reflect relevant diversity		historical control group	1. no effectiveness outcomes	
Goff (2014)	4. Enrolled populations do not reflect relevant diversity		no control group		
Magnani (2013)	2. Study population is unclear		no control group	1. no effectiveness outcomes	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gap assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use. 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 8. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Henricks (2019)	2 not randomized	1 not blinded			2, 3	
Henricks (2018)	2 not randomized	1 not blinded			2, 3	
Cremolini (2018)	2. convenience sample	1 not blinded			2, 3	2 no comparator
Deenen (2016)	2 not randomized	1 not blinded			2, 3	
Goff (2014)	2 convenience sample	1 not blinded			2, 3	2 no comparator
Magnani (2013)	2 convenience sample	1 not blinded			2, 3	2 no comparator

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Section Summary: Testing for DPYD or TYMS Variants Affecting 5-fluorouracil Dose Adjustment

A TEC Assessment (2010) concluded that *DPYD* and *TYMS* variant testing had a poor ability to identify patients likely to experience severe 5-FU toxicity. Since the publication of the TEC 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 one 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 OS, 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.

Summary of Evidence

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-FU AUC, the evidence includes RCTs, observational studies, and systematic reviews. The relevant outcomes are OS, disease-specific survival, test accuracy and validity and treatment-related morbidity. Several analyses of patients with CRC 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 BSA-based monitoring and no significant difference in toxicity. Most observational data were derived from studies conducted in the 1980's when different

chemotherapy protocols were used. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

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. The 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 one 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 OS, 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

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. CPIC (2013) published evidence-based guideline for *DPYD* genotype and fluoropyrimidine dosing.(19) The guidelines did not address testing.

An update to the Clinical Pharmacogenetics Implementation Consortium (2017) guidelines was published by Amstutz et al (2018).(34) As in 2013, the primary focus of the guidelines was on the DPYD genotype and implications for dosing of fluoropyrimidine. In the 2017 update, CPIC 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 CPIC listed the c.1905+1G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-FU toxicity. Additional alleles potentially associated with 5-fluorouracil toxicity were added in online updates to the guideline's tables in 2020.(35) 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-FU-based treatments, or exclude them, depending on the patient’s level of DPYD activity. CPIC advised follow-up therapeutic drug monitoring to guard against under dosing and cautioned that genetic tests could be limited to known risk variants and, therefore, not identify other *DPYD* variants.

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.(36) 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 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 patients with early or advanced colorectal cancer and patients with squamous cell carcinoma of head-and-neck cancer receiving common 5-fluorouracil dosing regimens.

National Comprehensive Cancer Network Guidelines

National Comprehensive Cancer Network does not recommend use of area under the curve guidance for 5-fluorouracil (5-FU) dosing or genetic testing for *DPYD* and/or *TYMS* variants in patients with colon,(37) rectal,(38) breast,(39) gastric,(40) pancreatic cancer,(41) or head and neck cancers.(42)

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 DYPD variants are necessarily associated with this risk, universal pretreatment DPYD genotyping remains controversial and the NCCN Panel does not support it at this time."

National Institute for Health and Care Excellence

The National Institute of Health and Care Excellence (2014) published evidence-based diagnostics guidance on the MY5-FU assay for 5-FU chemotherapy dose adjustment.(43) The evidence for the guidance was reviewed in February 2018. The guidance stated, “The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

There are currently no relevant ongoing trials. Some unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
AUC-guided dosing of 5-FU			
NCT00943137	The Optimization of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer	55	Jun 2017 (waiting for results)
NCT02055560[a]	Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-FU Exposure Optimization Testing	350	Dec 2017 (waiting for results)
Testing for genetic variants affecting 5-fluorouracil dosing			

NCT00131599	Thymidylate Synthase Polymorphisms as a Predictor of Toxicity to 5-Fluorouracil Based Chemotherapy in Stage III Colon Cancer	104	July 2017
NCT04269369	Implementation of Pre-emptive Geno- and Phenotyping in 5-Fluorouracil- or Capecitabine-treated Patients	250	Sep 2021
NCT05266300	Implementation and Quality Assurance of DPYD-genotyping in Patients Treated with Fluoropyrimidines	722	Oct 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations
National and Local:

There is no national or local coverage determination addressing on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/22/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/11	8/16/11	9/8/11	Joint policy established
7/1/12	4/10/12	5/18/12	New code added, S3722
9/1/13	6/19/13	6/26/13	New codes added: 81400 and 81401; no change in policy status
3/1/15	12/9/14	12/29/14	Policy updated to reflect new test name, My5-FU™. Added TheraGuide® testing for genetic mutations in DPYD or TYMS. This testing is experimental/ investigational. Policy title changed from "Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Cancer" to "Genetic and Laboratory Testing for Use of 5-Fluorouracil in Patients with Cancer." References and rationale updated.
7/1/16	4/19/16	4/19/16	• References and rationale updated • Removed TheraGuide® from medical policy statement as this test is no longer commercially available.
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Added code 81327
11/1/18	8/21/18	8/21/18	• Routine maintenance • Added codes 81232, and 81346 • Deleted codes 81327, 81400, 81401, and 84999
11/1/19	8/20/19		Routine maintenance
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		Routine maintenance
3/1/23	12/20/22		Routine maintenance (slp)

3/1/24	12/19/23		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC AND LABORATORY TESTING FOR USE OF 5-FLUOROURACIL IN PATIENTS WITH CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.