2.04.68	Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer		
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Section:	2.0 Medicine	**Page:**	Page 1 of 20

Policy Statement

My 5-fluorouracil™ assay testing or other types of assays for determining 5-fluorouracil (5-FU) 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 dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) genes to guide 5-fluorouracil dosing and/or treatment choice in patients with cancer is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following specific CPT codes may be used:

- **81230**: CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
- **81231**: CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)
- **81232**: DPYD (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (e.g., *2A, *4, *5, *6)
- **81346**: TYMS (thymidylate synthetase) (e.g., 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (e.g., tandem repeat variant)

The following is a specific HCPCS "S" code for the My5-FU test:

- **S3722**: Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil

Description

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.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the

time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

Background

5-fluorouracil

The agent 5-fluorouracil is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (*TYMS*) enzyme, which is involved in DNA production. 5-fluorouracil has been used for many years to treat solid tumors (e.g., colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 4 toxicity (i.e., mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-fluorouracil. Several studies also have reported statistically significant positive associations between 5-fluorouracil exposure and tumor response. In current practice, however, 5-fluorouracil dose is reduced when symptoms of severe toxicity appear but is seldom increased to promote efficacy.

Based on known 5-fluorouracil pharmacology, it is possible to determine a sampling scheme for the area under the curve determination and to optimize an area under the curve target and dose-adjustment algorithm for a particular 5-fluorouracil chemotherapy regimen and patient population. For each area under the curve value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target area under the curve without overshooting and causing severe toxicity.

In clinical research studies, 5-fluorouracil 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.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of the condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: relevance, and quality and credibility. To be relevant,

studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The primary goal of therapeutic drug monitoring, pharmacogenomics testing, and personalized medicine is to achieve better clinical outcomes compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease- related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the therapeutic drug monitoring strategy or pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

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

Clinical Context and Therapy Purpose

The purpose of laboratory testing in patients with cancer for whom 5-fluorouracil is indicated is to use test results to guide 5-fluorouracil dosing so that the therapeutic impact is maximized and the toxicity is decreased.

The question addressed in this evidence review is: Does laboratory testing for 5-fluorouracil area under the curve improve the net health outcome in individuals with cancer?

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The test being considered is laboratory assays to determine 5-fluorouracil area under the curve.

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 metabolism. 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. In the U.S., a commercial immunoassay (My5-fluorouracil) can quantify plasma 5-fluorouracil concentration from a blood sample drawn during continuous infusion at steady state (18-44 hours after the start of infusion) and provide a dose-adjustment algorithm to maintain plasma 5-fluorouracil area under the curve between 20 and 30 mg/h/L during the next cycle.[1,]

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.[2,3,]

Comparators
The following practice is currently being used to make decisions about dosing of 5-fluorouracil: standard dosing by body weight, specifically BSA-based dosing.

Body surface area-based dosing is associated with wide variability in pharmacokinetic parameters leading to significant differences in individual exposure. Nevertheless, BSA-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-fluorouracil 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 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 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][4,] and Fety et al [1998][5,]), as well as from 3 observational studies.[6,] In a pooled analysis, the overall response rate was significantly higher with pharmacokinetic area under the curve-monitored 5-fluorouracil therapy than with standard BSA-based monitoring (odds ratio, 2.04; 95% confidence interval, 1.41 to 2.95). In terms of toxicity, the incidence of diarrhea (3 studies), neutropenia (3 studies), and hand-foot syndrome (2 studies) did not differ significantly between the pharmacokinetic and body surface area monitoring strategies. The rate of mucositis was significantly lower in the body surface area-monitored group (3 studies; odds ratio, 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 3 RCTs, 2 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).[7,] 5-fluorouracil was dosed using BSA 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 body surface area 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 (2008) 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 area under the curve-targeted dosing (by high-performance liquid chromatography) for single-agent 5-fluorouracil compared with fixed dosing.[4] 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%).[8,9] In the latter 2 trials, the delivery over a longer time period for both 5-fluorouracil (22 hours vs. 8 hours) and leucovorin (2 hours vs. bolus), which is characteristic of currently recommended 5-fluorouracil treatment regimens, likely minimized toxicity. The administration schedule used in the Gamelin et al (2008) trial[4] is rarely used in clinical practice and is absent from available guidelines.[3] Additional optimization studies would be needed to apply 5-fluorouracil exposure monitoring and area under the curve-targeted dose adjustment to a more standard single-agent 5-fluorouracil treatment regimen, with validation in a comparative trial versus 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-fluorouracil exposures in head and neck cancer patients that were significantly reduced in the dose-adjustment arm compared with the fixed-dose arm.[5] This reduced toxicity but did not improve clinical response. The dose-adjustment method in this trial might have been too complex because the 12 patients with protocol violations in this treatment arm (of 61 enrolled) all were related to 5-fluorouracil dose adjustment miscalculations. Because patients with protocol violations were removed from the analysis, results did not reflect "real-world" results of the dose-adjustment method. Also, the induction therapy regimen used 2 drugs, not the current standard of 3 ; therefore, the 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)[7]	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)[4]	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)[5]	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; RCT: randomized controlled trial.

Table 2. Summary of Key Randomized Trials Results

Study	Toxicity	Overall Response Rate	Median Overall Survival or PFS
Deng et al (2020)[7]	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

Study	Toxicity		Overall Response Rate	Median Overall Survival or PFS
Gamelin et al (2008)[4]			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)[5]	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)[7]					
Gamelin et al (2008)[4]					
Fety et al (1998)[5]		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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[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)[7]	1. Selection not described	1. Not blinded				2. Comparison to other tests not reported
Gamelin et al (2008)[4]	1. Selection not described	1. Not blinded				2. Comparison to other tests not reported

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Fety et al (1998)[5.]	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.[10,11,12.] 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.[13,14.] Gamelin et al (1998) developed a chart for weekly dose adjustment based on the results of an earlier, similar single-arm study (1996)[15.] in which the 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 My5-fluorouracil assay in patients with colorectal cancer. 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 were from observational studies; most RCTs were conducted in the 1980s when different chemotherapy protocols were used.

Testing for *DPYD* or *TYMS* Variants Affecting 5-fluorouracil Dose Adjustment

Clinical Context and Therapy Purpose

The purpose of genetic testing in patients with cancer for whom 5-fluorouracil is indicated is to use test results to guide 5-fluorouracil dosing so that the therapeutic impact is maximized and the toxicity is decreased.

The question addressed in this evidence review is: Does genetic testing to guide 5-fluorouracil dosing improve the net health outcome in individuals with cancer?

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The test being considered is genetic testing for variants (e.g., in *DPYD* and *TYMS*) affecting 5-fluorouracil 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 dihydropyrimidine reductase (DPYD). Because DPYD is a saturable enzyme, the pharmacokinetics of 5-fluorouracil are strongly influenced by the dose and schedule of administration.[16] 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 codominantly inherited trait.[17]

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.[18] 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 (2 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-fluorouracil toxicity. Cancer types and specific variants differed across these reports.[19]-[24]

Comparators
The following practice is currently being used to make decisions about dosing of 5-fluorouracil: standard dosing by body weight, specifically 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-fluorouracil 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 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 overlapping populations were excluded.

Review of Evidence
A Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2010) concluded that *DPYD* and *TYMS* variant testing did not meet TEC criteria.[25] The Assessment noted that the tests had "poor ability to identify patients likely to experience severe 5-fluorouracil 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."[25]

Nonrandomized Studies

Several recent, prospective, observational studies have reported safety and effectiveness outcomes in patients who received genetic testing prior to receiving a 5-fluorouracil-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,[26,27,28] and 1 also included a matched-pairs analysis using previously-collected data.[27] The others were single-arm, uncontrolled studies.[29,30,31] 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.[27] Group 1 (n=40) were DPYD*2A carriers treated with an approximately 50% reduced fluoropyrimidine dose. Group 2 (n=1606) were wild-type patients who had been identified as part of an earlier study (Deenan et al [2016];[26] discussed below) and treated with a standard dose. Group 3 (n=86) were DPYD*2A carriers, identified from the literature, treated with a standard dose. Safety outcomes for the first 18 of the 40 patients in Group 1 were previously reported in Deenan et al (2016).[26] Patients in Group 1 were matched to those in Group 2 for the primary analysis for covariables known to influence treatment outcome. The primary effectiveness endpoint was overall survival. Secondary endpoints were progression-free survival and tumor response.

In matched-pair comparisons, Groups 1 and 2 did not differ on overall survival (hazard ratio 0.82; 95% confidence interval 0.47 to 1.43; p=0.47), progression free survival (hazard ratio 0.83; 95% confidence interval 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 1 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.[26] The study included cancer patients intending to undergo treatment with fluoropyrimidine-based therapy (5-fluorouracil or capecitabine).[26] 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% confidence interval, 10% to 53%) patients experienced grade 3 or higher toxicity. In historical controls with *DPYD*2A* variant alleles, the rate of grade 3 or higher toxicity was 73% (95% confidence interval, 58% to 85%). The historical controls were more likely to be treated with 5-fluorouracil 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.

Henricks et al (2018) conducted a prospective study of adult patients with cancer who were intended to start fluoropyrimidine-based therapy.[28] 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% confidence interval 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.

Cremolini et al (2018) [31] 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 received study treatments as planned; dosage was not adjusted based on genotyping. All patients received study treatments at planned doses. Overall 8 of 10 patients who were *DPYD* carriers experienced grade 3 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.[29] Twenty-five patients who had *TSER* 2R/2R or 2R/3R genotypes received a modified 5-fluorouracil 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 overall survival 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-fluorouracil or capecitabine) who underwent *DPYD* analysis for the *1905+1* G>A variant by high-performance liquid chromatography.[30] Four patients were heterozygous carriers. Of these, 3 patients received a 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 et al (2019)[27]	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

Study	Study Type	Country	Dates	Participants	Treatment
Henricks et al (2018)[27.]	Prospective, with historical control	Netherlands	2015-2017	Patients intended to be treated with FU-based chemotherapy (N =1181)	Genotyping for DPYD*2A,
Cremolini et al (2018)[31.]	Prospective, uncontrolled	Italy	2008-2011	Patients with metastatic colorectal cancer who were treated with 5-fluorouracil and irinotecan-based chemotherapy in an RCT (N =443)	Genotyping for DPYD*2A
Deenen et al (2016)[26.]	Prospective, with historical control	Netherlands	2007-2011	Patients intended to be treated with FU-based chemotherapy (N =2038)	Genotyping for DPYD*2A
Goff et al (2014)[29.]	Prospective, uncontrolled	U.S.	2008-2010	Adults with gastric or gastroesophageal junction cancer (N =25)	Genotyping for TSER tandem repeats
Magnani et al (2013)[30.]	Prospective, uncontrolled	Italy	2011-2012	Patients diagnosed with gastrointestinal, breast, head and neck, and other tumors (N =180)	DPYD analysis

DPYD: dihydropyrimidine reductase; FU: fluoropyrimidine; 5-fluorouracil: 5-fluorouracil; RCT: randomized controlled trial.

Table 6. Summary of Key Nonrandomized Trials Results

Study	Heterozygous Carrier Patients	Grade 3 Toxicity	Overall Response Rate	Median Overall Survival
Henricks et al (2019)[27.];				
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 20.82 (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 et al (2018)[28.]			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 et al (2018)[31.]	10/439 (2.2%)	8/10 (80%)	NR	NR
Deenen et al (2016)[26.]	22/2038 (1.1%)	28%	NR	NR
P-value		<0.001		
Goff et al (2014)[29.]	NR	NR	39.1% (9 partial responses, no complete responses)	11.3 months; 6.2 months
95% CI			22.2-59.2	
Magnani et al (2013)[30.]	4 (2.2%)	NR	NR	NR

CI: confidence interval; NR: not reported; NA: not applicable; 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 et al (2019)[27.]			historical control group		
Henricks et al (2018)[27.]			historical control group	1. no effectiveness outcomes	
Cremolini et al (2018)[31.]		3. genotype-based dosing not used	no control group	1. no effectiveness outcomes	
Deenen et al (2016)[26.]			historical control group	1. no effectiveness outcomes	
Goff et al (2014)[29.]			no control group		
Magnani et al (2013)[30.]			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 gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[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 et al (2019)[27.]	2. not randomized	1. not blinded			2., 3.	
Henricks et al (2018)[28.]	2. not randomized	1. not blinded			2., 3.	
Cremolini et al (2018)[31.]	2. convenience sample	1. not blinded			2., 3.	2. no comparator
Deenen et al (2016)[26.]	2. not randomized	1. not blinded			2., 3.	
Goff et al (2014)[29.]	2. convenience sample	1. not blinded			2., 3.	2. no comparator
Magnani et al (2013)[30.]	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 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 with other tests not reported.

Section Summary: Testing for *DPYD* or *TYMS* Variants Affecting 5-fluorouracil Dose Adjustment
A 2010, TEC Assessment concluded that *DPYD* and *TYMS* variant testing had a poor ability to identify patients likely to experience severe 5-fluorouracil 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 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.

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 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 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 (e.g., 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 TEC Assessment (2010) concluded that *DPYD* and *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
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 colon[32], 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 *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."

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 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.

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			
Area under the curve-guided dosing of 5-fluorouracil			
NCT00943137	The Optimisation of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer	55	June 2017
NCT02055560[a]	Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-fluorouracil Exposure Optimization Testing	350	Dec 2017 (unknown)

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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)
	81232	DPYD (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (e.g., *2A, *4, *5, *6)
	81346	TYMS (thymidylate synthetase) (e.g., 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (e.g., tandem repeat variant)
HCPCS	S3722	Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/30/2015	BCBSA Medical Policy adoption
06/01/2016	Policy revision without position change
05/01/2017	Policy revision without position change
02/01/2018	Coding update
05/01/2018	Policy revision without position change
05/01/2019	Policy revision without position change
10/01/2019	Policy revision without position change
06/01/2020	Annual review. No change to policy statement. Literature review updated.
05/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of

services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer 2.04.68 **Policy Statement:** My 5-fluorouracil™ assay testing or other types of assays for determining 5-fluorouracil (5-FU) 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 dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) genes to guide 5-fluorouracil dosing and/or treatment choice in patients with cancer is considered **investigational**.	**Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer 2.04.68** **Policy Statement:** My 5-fluorouracil™ assay testing or other types of assays for determining 5-fluorouracil (5-FU) 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 dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) genes to guide 5-fluorouracil dosing and/or treatment choice in patients with cancer is considered **investigational**.