



Louisiana

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

Policy # 00291

Original Effective Date: 03/16/2011

Current Effective Date: 08/15/2018

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers My5-FU^{™†} testing or other types of assays for determining 5-fluorouracil (5-FU) area under the curve (AUC) in order to adjust 5-FU dose for colorectal cancer (CRC) patients or other cancer patients to be **investigational**.*

Based on review of available data, the Company considers testing for genetic variants in dihydropyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) to guide 5-FU dosing and/or treatment choice in patients with cancer to be **investigational**.*

Background/Overview

5-FLUOROURACIL

The agent 5-FU is a widely used antineoplastic chemotherapy drug that targets TYMS enzyme, which is involved in deoxyribonucleic acid (DNA) production. 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 3 or 4 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 AUC determination and to optimize an AUC target and dose-adjustment algorithm for a particular 5-FU chemotherapy regimen and patient population. 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.

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Measuring Exposure to 5-FU

Laboratory Testing

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

Determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the United States, a commercial immunoassay (My5-FU) can quantify plasma 5-FU 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-FU AUC between 20 and 30 mg/h/L during the next cycle.

Genetic Testing

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

Catabolism of 5-FU is controlled by the activity of *DPYD*. Because *DPYD* is a saturable enzyme, the pharmacokinetics of 5-FU are strongly influenced by the dose and schedule of administration. For example, 5-FU clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic variants in *DPYD*, located on chromosome 1, can lead to reduced 5-FU 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.

The anabolic pathway metabolizes 5-FU to an active form that inhibits DNA and RNA synthesis by competitive inhibition of *TYMS* or by incorporation of cytotoxic metabolites into nascent DNA. 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-FU resistance due to increased tumor *TYMS* expression compared with the *TSER**2 variant (2 tandem repeats) and wild-type forms.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. My5-FU (Saladax Biomedical) and genetic testing for variants in *DPYD* and *TYMS* for predicting the risk of 5-FU toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer

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laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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

Clinical Context and Proposed Clinical Utility

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

The question addressed in this evidence review is: Can lab tests be used to guide 5-FU dosing to maximize therapeutic impact and minimize toxicity?

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

Patients

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 AUC.

Comparators

The following practice is currently being used to make decisions about dosing of 5-FU. This involves standard dosing by body weight, specifically body surface area (BSA)-based dosing.

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Outcomes

The outcomes of interest are reductions in treatment-related morbidity related to 5-FU toxicity. Types of severe toxicity include neutropenia, diarrhea, mucositis, and hand-foot syndrome.

Timing

Specific survival outcomes may vary by type of cancer, but generally 1- to 2-year survival is a short-term outcome and 5- and 10-year survival is a long-term outcome. Treatment-related morbidity can be acute toxicity (≤ 14 days) or late toxicity (> 14 days).

Setting

Patients would be tested in the oncology setting.

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Kline et al (2014) assessed My5-FU in a retrospective study of patients with stage II and III (n=35) or stage IV or recurrent (n=49) CRC who received 5-FU regimens at a single center in the United States. Thirty-eight patients chose pharmacokinetic monitoring with OnDose and 46 patients were dosed by BSA. Median progression-free survival did not differ by dosing strategy in stage IV or recurrent patients (14 months with AUC monitoring vs 10 months BSA dosing; p=0.16) but did differ in stage II and III patients (p=0.04). Thirty-seven percent of stage IV or recurrent patients in both dosing strategy groups experienced grade 3 toxicity. Among stage II and III patients, 32% of AUC-monitored patients and 69% of BSA-dosed patients experienced grade 3 toxicity (p=0.04). The onset of adverse events also was delayed in the AUC-monitored group (6-7 months) compared with the BSA-dose group (2 months; p=0.01).

My5-FU was clinically validated for patients with CRC in an observational analysis reported by Saam et al (2011). Sequential patients (N=357) were treated with constant infusion 5-FU using current adjuvant or metastatic treatment protocols with or without bevacizumab. Samples were drawn at least 2 hours after the start of and before the end of each infusion and sent for analysis. Sixty-two (17%) patients were studied longitudinally across 4 sequential sample submissions (i.e., four 5-FU treatment infusions), of which 3 (5%) were within the target AUC after the first infusion. By the fourth infusion, this percentage rose to 37%, and outliers were reduced. Use of bevacizumab did not affect results. Response and toxicity were not reported.

Section Summary: Clinically Valid

Several analyses of patients with CRC have evaluated the clinical validity of the My5-FU assay. In one study, the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring vs BSA monitoring, but progression-free survival did not differ between groups in patients with stage IV or recurrent cancer. In another study, among patients studied longitudinally and monitored with My5-FU, 3% were within the target AUC after the first infusion, and this reached 37% by the fourth infusion.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

The results of single-arm trials of AUC-targeted 5-FU dose adjustment in advanced CRC patients have suggested consistently improved tumor response. Similar, although less compelling, results were seen in

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single-arm trials of AUC-targeted 5-FU dosing in head and neck cancer. The best contemporary evidence supporting AUC-targeted dosing consists of 2 RCTs, one enrolling patients with CRC and the other patients with head and neck cancer. No trials of any design were identified for 5-FU dose adjustment in other malignancies.

Gamelin et al (1998) developed a chart for weekly dose adjustment based on the results of an earlier, similar single-arm study (1996) in which dose was increased by prespecified increments and intervals up to a maximum dose or the first signs of toxicity. In an RCT enrolling patients with metastatic CRC, 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 AUC-targeted dosing (by high-performance liquid chromatography) for single-agent 5-FU compared with fixed dosing. 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%). In the latter 2 trials, 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 2008 Gamelin trial is rarely currently used in clinical practice and is absent from current guidelines. 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. 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-FU 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 three, and, therefore, the generalizability of results to current clinical practice is limited.

Yang et al (2016) published a meta-analysis of data from the 2 RCTs described above (i.e., Gamelin et al [2008] and Fety et al [1998]), as well as from 3 observational studies. 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, 2.04; 95% confidence interval [CI], 1.41 to 2.95). In terms of toxicity, the 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 (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.

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Section Summary: Clinically Useful

No RCTs or nonrandomized comparative studies were identified comparing health outcomes in cancer patients who did and did not have 5-FU dose adjustment using the My5-FU assay and who were treated with 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 data were from observational studies; RCTs were conducted in the 1980s when different chemotherapy protocols were used.

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

Clinical Context and Proposed Clinical Utility

The proposed clinical utility 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 question addressed in this evidence review is: Can genetic tests guide 5-FU dosing so to maximize therapeutic impact and minimize toxicity?

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

Patients

The relevant population of interest is 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.

Comparators

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

Outcomes

The outcomes of interest are reductions in treatment-related morbidity related to 5-FU toxicity. Types of severe toxicity include neutropenia, diarrhea, mucositis, and hand-foot syndrome.

Timing

Specific survival outcomes may vary by type of cancer, but generally 1- to 2-year survival is a short-term outcome and 5- and 10-year survival is a long-term outcome. Treatment-related morbidity can be acute toxicity (≤ 14 days) or late toxicity (> 14 days).

Setting

Patients would be tested in the oncology setting. Also, referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Toxicity

A number of studies have evaluated the association between variants in the *DPYD* and/or *TYMS* genes and 5-FU toxicity. Cancer types and specific variants studied differed across these reports. Several meta-analyses have been published. Li et al (2014) identified 7 cohort studies with a total of 946 patients with CRC. A pooled analysis of study findings found that *DPYD* variants correlated significantly with an increased risk of 5-FU-related toxicity. Also, Rosmarin et al (2014) identified 16 studies with a total of 4855 patients with CRC who were treated with capecitabine and other fluorouracil-based treatment regimens. Capecitabine toxicity was significantly associated with several *DPYD* alleles and several *TYMS* single nucleotide variants.

A key study was published by Schwab et al (2008). Trialists enrolled 683 patients who were receiving 5-FU for colon or other gastrointestinal cancers, cancers of unknown primary, or breast cancer in a genotype study. Seven different 5-FU regimens (monotherapy or in combination with folate or levamisole [not approved by the FDA]) administered by bolus or by infusion were included. Patients were genotyped for the *DPYD* splice site variant *DPYD*2A* (*IVS14+1G>A*), which leads to a nonfunctional enzyme, and for *TYMS* tandem repeats. Sensitivity, specificity, and positive and negative predictive values for overall toxicity, diarrhea, mucositis, and leukopenia were calculated (see Table 1). Although heterozygosity for *DPYD*2A* had 99% specificity for serious toxicity, sensitivity ranged from 6% to 13%. Tandem repeats in *TYMS* were neither sensitive nor specific indicators of serious toxicity. Clinical factors also were examined for association with toxicity. Overall and in the group of 13 patients who were heterozygous for *DPYD*2A*, women were more likely than men to develop severe toxicity (overall odds ratio, 1.9; 95% CI, 1.26 to 2.87; $p=0.002$), most commonly mucositis. Bolus administration of 5-FU was a significant, independent predictor of severe toxicity overall.

Table 1. Grade 3 and 4 Adverse Events and *DPYD* and *TYMS* Genotypes

Toxicity	<i>DPYD*2A</i> ^a (n=13), %	<i>TYMS</i> VNTR 2/3 or 3/3 ^b (n=521), %
Overall toxicity		
Sensitivity	6	65
Specificity	99	21
Positive predictive value	46	14
Negative predictive value	85	76
Diarrhea		

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Toxicity	<i>DPYD</i> *2A ^a (n=13), %	<i>TYMS</i> VNTR 2/3 or 3/3 ^b (n=521), %
Sensitivity	NR	57
Specificity	NR	22
Positive predictive value	NR	6
Negative predictive value	NR	84
Mucositis		
Sensitivity	8	NR
Specificity	99	NR
Positive predictive value	31	NR
Negative predictive value	93	NR
Leukopenia		
Sensitivity	13	NR
Specificity	99	NR
Positive predictive value	31	NR
Negative predictive value	96	NR

Adapted from Schwab et al (2008).

NR: not reported; VNTR: variable number of tandem repeats.

^a Heterozygous *DPYD**2A vs wt/wt.

^b Homozygous (3R/3R) or mixed heterozygous (2R/3R) triple repeats vs homozygous double repeats (2/2).

Boige et al (2016) published a subgroup analysis of patients participating in an RCT. The RCT compared treatment with FOLFOX4 and FOLFOX4 plus cetuximab. A total of 1545 patients, participated in the pharmacogenetics subgroup study and were genotyped on 25 *DPYD* variants. The primary endpoint was the development of grade 3 or higher 5-FU-related adverse events (hematologic and gastrointestinal combined). Two *DPYD* variants (D949V, V73231) were significantly associated with grade 3 or higher adverse events (p<0.001 for both).

Vásquez et al (2017) prospectively evaluated 197 patients who were treated with 5-FU between 2013 and 2015. All patients were given the European Organization for Research and Treatment of Cancer quality of life assessment; there was a significant link between low European Organization for Research and Treatment of Cancer scores and the patient's risk of developing severe toxicity. However, no significant association between variants in methylenetetrahydrofolate reductase (*MTHFR*) or *TYMS* tandem repeats and severe toxicity could be identified.

Nahid et al (2017) prospectively evaluated 161 patients with CRC who were treated with 5-FU based chemotherapy. Of these patients, clinical follow-up was available for 139 patients. Within this population, *DPYD**2A was significantly associated with grade 3 or 4 toxicity (p=0.023). The *MTHFR* C677T variant was associated with increased efficacy of treatment (p=0.006). The authors recommended confirmation of these findings in a larger population.

Efficacy

A meta-analysis by Wang et al (2013) included 11 studies that assessed the association between *TYMS* variants (5' tandem repeats and a single nucleotide substitution [G>C] within triplet repeats) and survival

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outcomes. Patients had gastric cancer or CRC and received 5-FU with or without leucovorin with or without levamisole. Three studies (n=311 patients) were eligible for pooled analysis of overall survival (OS). Statistical heterogeneity was not assessed. Patients who were homozygous for triplet repeats (3R/3R) had longer OS than patients who were homozygous for doublet repeats (2R/2R) or compound heterozygous (2R/3R).

Smyth et al (2017) published a randomized phase 3 trial of 456 patients treated for gastroesophageal cancer either with surgery alone or with surgery augmented with 5-FU chemotherapy. Of these patients, genetic tests were performed for 289 patients. The primary outcome was any association between 10 germline variants, including tandem repeats in the *TYMS* gene, and response rates, survival, or toxicity. Of the genes evaluated, none showed a variant significantly associated with chemotherapy-related toxicity. Of patients who received chemotherapy, there was a significant association between the *TYMS* 2R/2R genotype and longer survival: for these patients, median OS was not reached during the study, while patients with *TYMS* 2R/3R or 3R/3R genotypes, respectively, had a median OS of 1.44 or 1.60 years (p=0.005). Trialists noted that patients with *TYMS* 2R/2R genotype seemed to benefit from the chemotherapy treatment, with a significant interaction between treatment arm and genotype (p=0.029). No relationship between genotype and chemotherapy toxicity was noted. The trial was limited by the lack of tissue samples for all patients.

Section Summary: Clinically Valid

A number of observational studies and meta-analyses of these studies have found that *DPYD* variants and/or *TYMS* single nucleotide variants correlated significantly with an increased risk of 5-FU-related toxicity. A meta-analysis of 3 studies found a significant association between *TYMS* gene variants and longer OS. In a separate study, a different variant of *TYMS* was significantly associated with longer OS. The available studies reported statistical associations and did not prospectively evaluate health outcomes in patients with genetic variants.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A TEC Assessment (2010) concluded that *DPYD* and *TYMS* variant testing did not meet TEC criteria. 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.”

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No prospective trials comparing efficacy and safety outcomes with or without pretreatment *DPYD* and/or *TYMS* testing were identified.

One prospective trial compared outcomes for pretreatment *DPYD**2A testing with historical controls. This study by Deenen et al (2016) included cancer patients intending to undergo treatment with fluoropyrimidine-based therapy (5-FU or capecitabine). 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., $\geq 50\%$) 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 3 or higher toxicity. In historical controls with *DPYD**2A variant alleles, the rate of grade 3 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.

Goff et al (2014) prospectively genotyped 42 adults who had gastric or gastroesophageal junction cancer for *TSER* tandem repeats. 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-performance liquid chromatography. 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.

Section Summary: Clinically Useful

A Technology Evaluation Center (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. A study comparing outcomes after pretreatment *DYPD* testing and historical controls found a lower rate of grade 3 or higher toxicity in patients who underwent genetic testing. That study was limited by lack of randomization and absence of a concurrent control group.

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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. 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. One study, for example, found that the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring vs BSA monitoring, but progression-free survival did not differ between groups in patients with stage IV or recurrent cancer. No RCTs or nonrandomized comparative studies were identified comparing health outcomes in cancer patients who did and did not have 5-FU dose adjustment using the My5-FU assay and who were treated with 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 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 the effects of the technology on 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. Relevant outcomes are OS, 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. One study compared outcomes in patients undergoing pretreatment *DPYD* testing with historical controls who did not receive testing. In that study, rates of grade 3 or higher toxicity were lower in patients who had genetic testing; however, the study was not randomized and lacked concurrent controls. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date:	03/16/2011
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03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. New Policy.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Investigational OnDose statement modified to reflect new test name, My5-FU. Investigational statement for TheraGuide testing for genetic mutations in <i>DPYD</i> or <i>TYMS</i> added. Title changed from "Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Patients Administered 5-FU for Cancer" to "Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer" to reflect incorporation of new test.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Removed TheraGuide test from policy statement as it is no longer available.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Genetic testing nomenclature updated. "Mutations" changed to "variants" throughout the policy. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review

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08/15/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 Next Scheduled Review Date: 08/2019

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HCPCS	S3722
ICD-10 Diagnosis	All related diagnoses

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