# Genetic and Laboratory Testing for 5-fluorouracil (5-FU) Sensitivity



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## DESCRIPTION

Dihydropyrimidine dehydrogenase (DPD) is the first of three enzymes in the fluoropyrimidine metabolic pathway and limits the enzyme in fluorouracil (5-FU). Individuals with DPD deficiency are known to have a number of changes (e.g., mutations polymorphisms, variants) in the DPYD gene which are associated with loss or deficiency of DPD leading to fluoropyrimidine toxicity. Because DPD has the ability to break down fluoropyrimidines this carries a substantially increased risk of severe toxicity. DPYD is a saturable enzyme, because of this the pharmacokinetics of 5-FU are strongly influenced by the dose and schedule of administration.

Fluoropyrimidines include 5-fluorouracil (5-FU, Adrucil®) and capecitabine (Xeloda®). Fluoropyrimidines (5-Fluoroucil (5-FU) and its derivative capecitabine) are widely used antineoplastic chemotherapy drugs. 5-FU has been used for many years to treat solid tumors. Treatment is mostly administered after an examination which typically doesn't take into consideration any individual particularities, whether genetic or epigenetic.

Among potential toxicity risk factors one can find individual metabolic differences linked to genetic modifications of metabolism enzymes as well as differences in the chemical receptors and transporters. Although the benefits of 5-fluoroucil-based therapy is prolonging survival, major side effects are seen in many individuals receiving the drugs.

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 (e.g., neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Typically, individuals with DPD deficiency usually develop severe side effects after the first few doses of fluorouracil or capecitabine. To avoid the risk of severe and potentially fatal reactions, the manufactures of both 5-FU and the oral fluoropyrimidine recommend that the drugs are contraindicated in individuals with known DPD deficiency.

Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-FU:
(1) dosing based on determined area under the curve serum concentration target
(2) genetic testing for variants affecting 5-FU metabolism. Currently available polymerase chain reaction tests assess specific variants in genes encoding dihydropyrimidine reductase (DPYD) and thymidylate synthase (TYMS) in the catabolic and anabolic pathways of 5-FU metabolism there are several testing options for DPYD genotype, although, at present most test only for the DPYD 2A variant. Approximately 10% of individuals receiving fluoropyrimidines have severe side effects from fluorouracil and capecitabine. But not everyone has a DPD deficiency. The testing to determine the likelihood of intolerance is unreliable at this time.

**Pathophysiology**
Dihydropyrimidine dehydrogenase (DPD) enzyme – encoded by DPYD gene, is an enzyme which catabolizes > 80% of 5-FU into an inactive form that is eliminated in the urine (rate limiting enzyme). Reduced DPD activity can lead to the accumulation of active 5-FU metabolite, increasing the risk for 5-FU toxicity.

Thymidylate synthase (TYMS) enzyme – encoded by TYMS gene, is the primary target for 5-FU. The remaining 5-FU drug is metabolized by different enzymes into an active form that inhibits the synthesis of DNA and RNA by competitive inhibition of TYMS or by direct incorporation of cytotoxic metabolites into nucleic acids. TYMS gene variants result in reduced expression of TYMS and may be associated with higher clinical responsiveness to 5-FU therapy and increased risk of toxicity.

Lack of detection of the targeted DPYD and TYMS variants does not rule out risk for 5-FU toxicity or predict degree of responsiveness to 5-FU.

**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 improve the net health outcome in individuals at risk for fluorouracil toxicity?

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

**Populations**
The relevant population of interest is individuals who have an indication for 5-fluorouracil toxicity and chemotherapeutic response testing.

**Interventions**
The test being considered is laboratory assays to determine 5-fluorouracil toxicity and chemotherapeutic response testing. (eg, Genetic variants DPYD and TYMS)

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.

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

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. 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 (eg, IVS14+1G>A [also known as DPYD*2A], 2846A>T [D949V]). DPYD deficiency is an autosomal codominantly inherited trait.

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.

**Comparators**
The following practice is currently being used to make decisions about dosing of 5-fluorouracil: standard dosing by body weight (e.g., 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.

**Review of Evidence**
(2020; Review Current though 02/2022) UptoDate Saif et al. noted the influence of polymorphisms in dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme in FU catabolism, on cardiotoxicity is unclear. Severe toxic reactions to FU (myelosuppression, diarrhea, stomatitis, and neurotoxicity, which can be fatal) are associated with decreased levels of DPD enzyme activity, and several genetic variations in the gene encoding DPD (DPYD) result in decreased DPD enzyme activity.

**Laboratory Testing to Determine 5-fluorouracil Area Under the Curve for Dose Adjustment: Meta-Analysis**

(2016) Yang et al. published a meta-analysis of data from the 2 RCTs 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 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.

**Laboratory Testing to Determine 5-fluorouracil Area Under the Curve for Dose Adjustment: Randomized Controlled Trials**

(2020) Deng et al. conducted an RCT in patients with advanced colorectal cancer who were treated with 5-fluorouracil (FOLFOX or FOLFIRI). Patients identified were patients with advanced CRC intended to be treated with FU-based chemotherapy (N=153). 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. Limitations of the study reported are the selection was not described, it was not blinded, and no reported comparison tests.

(2008) Gamelin et al. 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. 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 two 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 is rarely used in clinical practice and is absent from available guidelines. 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. Additionally, noted limitations included no selection described, it was not blinded and no reported other comparison tests.

**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**

(2010) A TEC Assessment 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-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."

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

(2019) Henricks et al. included three comparison groups in a prospective cohort study in which patients received genotyping prior to treatment as part of routine care. 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]; 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). 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.

(2018) Cremolini et al. 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.

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

(2016) Deenan et al. compared outcomes for pretreatment DPYD*2A testing with historical controls. The study included cancer patients intending to undergo treatment with fluoropyrimidine-based therapy (5-fluorouracil 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., ≥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.

(2014) Goff et al. 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-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.

(2013) Magnani et al. 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. Four patients were heterozygous carriers. Of these, three 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.

**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 variant testing affecting 5-fluorouracil metabolism. 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. As a result, the Clinical Pharmacogenomics Implementation Consortium (CPIC) has made specific recommendations for fluoropyrimidine dosing for individuals with certain DPYD variants. However, the clinical sensitivity (10%) of DPYD testing for predicting severe toxicity in patients taking 5-FU or capecitabine is very low. Research suggests that other biomarkers, such as uracil or 5-FU degradation rate (FUDR) testing, are 20% (uracil) and 18% (FUDR) clinically more sensitive. Some report these tests can usually be performed quickly and at lower cost than DPYD testing but there is no evidence that adding DYPD variant analysis to either of these tests offers an incremental increase in clinical sensitivity. Sending a sample out for genetic testing may cause an unnecessary delay in starting antineoplastic therapy and additional cost. 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.
Key practice guidelines for cancer treatment do not support routine DPYD testing to assess for potential 5-fluorouracil toxicity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

**Professional Guidelines and Position Statements**

**Clinical Pharmacogenetics Implementation Consortium**
(2017) An update to the Clinical Pharmacogenetics Implementation Consortium noted 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. (*Accessed March 2022*)

**International Association of Therapeutic Drug Monitoring and Clinical Toxicology**
(2019) The International Association of Therapeutic Drug Monitoring and Clinical Toxicology published recommendations for therapeutic drug monitoring of 5-fluorouracil therapy. 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. (*Accessed March 2022*)

**National Institute of Health and Care Excellence (NICE)**
(2014; Last Reviewed 2018) The NICE published evidence-based diagnostics guidance on the 5-fluorouracil assay for 5-fluorouracil chemotherapy dose adjustment.

- 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." (*Accessed March 2022*)

**National Comprehensive Cancer Network**

- **Breast Cancer**
  - (Version 2.2022) No recommended guidance for the use of 5-fluorouracil genetic testing for DPYD and/or TYMS variants in individuals with breast cancer noted. (*Accessed March 2022*)
- **Colon Cancer**
  - (Version 1.2022) 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." (*Accessed March 2022*)
- **Gastric Cancer**
  - (Version 2.2022) No recommended guidance for the use of 5-fluorouracil genetic testing for DPYD and/or TYMS variants in individuals with gastric cancer noted. (*Accessed March 2022*)
- **Head and Neck Cancers**
  - (Version 1.2022) No recommended guidance for the use of 5-fluorouracil genetic testing for DPYD and/or TYMS variants in individuals with head and neck cancer noted. (*Accessed March 2022*)

- **Pancreatic Adnocoarinoma**
    - (Version 1.2022) No recommended guidance for the use of 5-fluorouracil genetic testing for DPYD and/or TYMS variants in individuals with pancreatic cancer noted. (*Accessed March 2022*)
- **Rectal Cancer**
    - (Version 1.2022) Patient in the United Stated (U.S.) have been shown to have greater tocity with fluorouracil. The dose of fluorouracil (2,400 $mg/m^2$ over 46 hours) is a starting cose consistent with the dose recommended in FLOFOX or FOLFIRI and should be strongly considered for U.S. patients.
    - FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 $mg/m^2$ over 48 hours).
    - No additional recommended guidance for the use of 5-fluorouracil dosing or genetic testing for DPYD and/or TYMS variants in individuals with rectal cancer noted. (*Accessed March 2022*)

**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). 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 as seen below. This is not an all-inclusive list:

- My5-fluorouracil™ (My5-FU) (Saladax Biomedical)
- TheraGuide® was offered by Myriad Genetics as a laboratory-developed test but has been discontinued.
- ARUP Laboratories offers a test that is equivalent to TheraGuide (5-FU toxicity and chemotherapeutic resonse, 7 mutations test).

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.

# PRIOR APPROVAL

Not applicable.

# POLICY

**Related Medical Policies:**
02.04.63 Expanded Genetic Panels to Identify Targeted Cancer Therapy

5-Fluorouracil (5-FU) toxicity and chemotherapeutic response testing is considered **investigational** for all indications due to a lack of evidence demonstrating an impact on improved net health outcomes.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81232 DPYD (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *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)
- S3722 Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil

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| POLICY HISTORY | | |
|---|---|---|
| **Date** | **Reason** | **Action** |
| April 2022 | Annual Review | Policy Revised |
| April 2021 | Annual Review | Policy Revised |
| April 2020 | Annual Review | Policy Revised |
| April 2019 | Annual Review | Policy Revised |
| April 2018 | | New Policy |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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