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Corporate Medical Policy

Testing for 5-Fluorouracil Use in Cancer Patients AHS-M2067

File Name:	testing_for_5_fluorouracil_use_in_cancer_patients
Origination:	1/2019
Last CAP Review	8/2021
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Last Review:	10/2021

Description of Procedure or Service

Chemotherapeutic agents are incredibly potent drugs, often carrying cytotoxic side effects. Most chemotherapeutic drugs have a steep dose-response relationship and a narrow therapeutic index (a range where an agent provides therapeutic effect without major side effects). Identification of the optimal dose of a chemotherapeutic agent, such as 5-fluorouracil, has been proposed as a potential improvement for the management of cancer patients (Eaton, 2021).

This policy does not address pharmacogenetic testing to aid or direct chemotherapies. For pharmacogenetic testing, please refer to AHS-M2021.

Related Policies:
Pharmacogenetic Testing AHS-M2021

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Testing for 5-fluorouracil use in cancer patients is not covered. BCBSNC will not reimburse for non-covered services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Testing for 5-Fluorouracil Use in Cancer Patients is covered

Not applicable.

When Testing for 5-Fluorouracil Use in Cancer Patients is not covered

Reimbursement is not allowed for testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer.

Reimbursement is not allowed for assays for determining 5-fluorouracil area under the curve in order to adjust 5-FU dosing for cancer patients, including but not limited to My5-FU.

Reimbursement is not allowed for uracil breath tests and dihydrouracil/uracil ratio testing of plasma, serum, or urine samples *to aid in managing dose adjustment in individuals undergoing 5-fluorouracil chemotherapy.*

Policy Guidelines

Chemotherapeutic agents encompass a wide variety of medications used to treat cancer. However, due to their cytotoxicity, these agents often have debilitating side effects such as nausea, vomiting, and more. Therefore, it can be useful to identify an "optimal" dose of these agents (for an individual patient), to maximize therapeutic efficacy and minimize harmful side effects. Numerous methods to identify an individual's optimal dose exist, such as body surface area (BSA)-based dosing, weight-based dosing, fixed-dose medications, and area-under-curve (AUC) dosing, which is generated by a curve of plasma concentration as a function of time. With both variables known, it would be possible to identify the exact amount of drug exposed to an individual instead of relying on clinical symptoms. AUC-based dosing is typically used for drugs cleared through glomerular filtration (such as carboplatin). However, AUC-based dosing is not usually applicable to most other anticancer agents as elimination of other drugs often involves several other pathways, thereby introducing additional variables that influence drug clearance (Eaton, 2021).

One common therapeutic agent is 5-fluorouracil, or 5-FU. Currently, 5-FU is administered intravenously as a continuous infusion; BSA-based dosage is often used to optimize treatment, and an AUC between 20 and 30 [mg×h×L] is recommended (Mindt et al., 2019). This particular chemotherapeutic agent can be used alone, or in a combinatory setting, to treat many types of cancer including breast, anal, stomach, colon, head, neck, and some skin cancers (Cancer_Research, 2019). Therapeutic drug monitoring (TDM), known as "the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens" (Kang & Lee, 2009), has shown promise in 5-FU based treatment regimens. In particular, the TDM practice has resulted in reduced toxicity and improved efficacy for the intravenous administration of 5-FU (Hashimoto et al., 2020).

Proprietary tests have been developed for identification of the optimal dose of several chemotherapeutic agents. Saladax Biomedical, under the product umbrella termed MyCare, offers a series of tests that aim to find the optimal dose for various chemotherapeutic agents. Their current catalog imatinib (MyImatinib). MyCare states that these tests will be able to guide dosing for these agents and minimize toxicity with only a blood test (MyCare, 2018a, 2018b). The test is intended for patients receiving 5-FU chemotherapy through intravenous infusion. The test takes plasma near the end of the infusion cycle and is based on the scattered light principle. The amount of scattered light varies inversely with the amount of 5-FU present in the plasma sample. The limit of detection is estimated at 52 ng/mL and the limit of quantitation is estimated at 85 ng/mL. A validated dose adjustment algorithm incorporates the measurements of 5-FU in plasma and uses AUC to calculate subsequent doses (NICE, 2014).

Additional tests have been proposed to aid in dosing and measuring toxicity in individuals undergoing chemotherapy. Since the efficacy of 5-FU depends on the enzyme dihydropyrimidine dehydrogenase (DPD), the concentration of uracil has been proposed to evaluate pyrimidine, including 5-FU, catabolism. The uracil breath test measures the concentration of carbon dioxide, a pyrimidine metabolic product, after an individual has ingested radiolabeled uracil (Cunha-Junior et al., 2013; Ezzeldin et al., 2009).

Analytical Validity

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

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However, when Cobas Integra 800 was compared to the other three clinical analyzers, only a proportional bias of ≤1.6% and a constant bias below the limit of detection was observed (Buchel et al., 2013).

Clinical Validity and Utility

Yang et al (2016) conducted a meta-analysis of data from 2 RCTs and 3 observational studies (654 patients) to compare the efficacy and toxicity of the use of pharmacokinetic (PK)-guided versus Body Surface Area (BSA)-based dose adjustment of 5-FU in advanced cancers. PK-monitored 5-FU therapy was associated with significant improvement in overall response rate (odds ratio = 2.04, compared with the traditional BSA method. The researchers concluded that "in comparison with conventional BSA method, PK-based 5-FU dosage confirmed a superior overall response rate and improved toxicities irrespective of significant difference, the results of which indicated that PK- monitored 5-FU dosage has the potential to be performed in colorectal cancer personalized therapy."

Fang et al. (2016) performed a meta-analysis to compare the BSA-based algorithm to a pharmacokinetic (PKG)-based algorithm for 5-fluorouracil (5-FU). Four studies (n = 504) were included. The authors found that the PKG algorithm "significantly" improved the objective response rate of 5-FU chemotherapy compared to the BSA-based algorithm. PKG was also found to "markedly" decrease the risk of grade 3/4 adverse drug reactions (Fang et al., 2016). Likewise, another study comparing 5-FU TDM to BSA-guided dosing results in patients with gastrointestinal cancer (n = 155) also reports greater interpersonal variability when using a BSA-guided strategy as compared to TDM (Morawska et al., 2018). A third study demonstrates that TDM can result in even greater improvements in elderly gastrointestinal cancer patients (older than 75 years old) as compared to younger patients (71% improvement in AUC vs. 50% improvement, respectively). This is significant considering that the majority of previous clinical trials excluded elderly patients (Macaire et al., 2019).

Wilhelm et al. (2016) evaluated the use of TDM to personalize 5-FU dosing in patients with colorectal cancer. Seventy-five patients were included. The authors aimed to achieve a target AUC of 20-30 mg x h/L and adjusted each cycle of 5-FU accordingly. The average AUC of 5-FU on the initial administration was "18 ± 6 mg × h/L, with 64%, 33%, and 3% of the patients below, within, or above the target AUC range, respectively." By the 4th administration, the average 5-FU AUC was 25 ± 7 mg × h/L, with 54% of patients within the target 5-FU AUC range. The incidence of 5-FU related side effects was reduced compared to historical data despite the increased dose. The authors concluded that "personalization of 5-FU dosing using TDM in routine clinical practice resulted in significantly improved 5-FU exposure and suggested a lower incidence of 5-FU-related toxicities" (Wilhelm et al., 2016).

Gamelin et al. (2008) conducted a study to compare conventional dosing of fluorouracil (FU) with pharmacokinetically guided FU dose adjustment in terms of response, tolerability, and survival. A total of 208 patients with measurable metastatic colorectal cancer were randomly assigned to two groups: group A (104 patients; 96 assessable), in which the FU dose was calculated based on body-surface area; and group B (104 patients; 90 assessable), in which the FU dose was individually determined using pharmacokinetically guided adjustments. Patients that received FU dose adjustment based on pharmacokinetic monitoring showed significantly improved objective response rate, a trend to higher survival rate, and fewer grade 3/4 toxicities. The researchers concluded that "these results support the value of pharmacokinetically guided management of FU dose in the treatment of metastatic colorectal patients" (Gamelin et al., 2008).

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

Joerger et al. built a pharmacokinetic-pharmacodynamic model of paclitaxel/carboplatin in ovarian cancer patients. Time above paclitaxel plasma concentration of 0.05 to 0.2 μmol/L (t_c> 0.05−0.2 μmol/L) is thought to be a good predictive marker for severe neutropenia and overall clinical outcome. A total of 139 patients were included in the study; each participant was given "175 mg/m2 over

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3 hours followed by carboplatin area under the concentration-time curve 5 mg/mL*min over 30 min." In 34 patients with measurable disease, objective response rate was 76%. Paclitaxel $t_c > 0.05$ μmol/L was found to be significantly higher in patients with a complete (t = 91.8 hours) or partial response (t = 76.3) compared to patients with progressive disease (t = 31.5). Paclitaxel t_c was also found to predict severe neutropenia well (Joerger et al., 2007).

A 2017 study by Moeung et al. (2017) evaluated the efficacy of TDM in patients (n = 89) with advanced germ cell tumors who receive high dose chemotherapy (TI-CE) as compared to using a formula-based covariate equation dosing method. The metric used to assess the efficacy of these two approaches was AUC for carboplatin. TDM was used on 58 of the patients for three days "to develop a covariate equation for carboplatin clearance prediction adapted for future TI-CE patients, and its performance was prospectively evaluated on the other 29 patients along with different methods of carboplatin clearance prediction." Using the developed covariate equation to determine dosing, the researchers showed that the mean AUC was 24.4 mg.min/ml per cycle with 10^{th} and 90^{th} percentiles of 22.4 and 26.8, respectively. They conclude, "TDM allows controlling and reaching the target AUC. Alternatively, the new equation of carboplatin clearance prediction, better adapted to these young male patients, could be used if TDM cannot be implemented" (Moeung et al., 2017). However, more recent studies have also shown that the method to determine carboplatin clearance (for example, glomerular filtration rate (GFR) versus estimated creatinine clearance (CrCl)) can have a significant effect on determining the actual AUC for carboplatin (Morrow, Garland, Yang, De Luna, & Herrington, 2019).

Guilhot et al. (2012) evaluated the correlation between "imatinib trough plasma concentrations (C_{min}) and clinical response and safety in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase in the Tyrosine Kinase Inhibitor OPtimization and Selectivity (TOPS) trial." Patients were randomized to 400 mg/day or 800 mg/day of imatinib. The authors found that the C_{min} was stable for patients in the 400 mg/day cohort but showed a slight decrease in the 800 mg/day cohort due to dose adjustments. The rates of major molecular response (MMR) and complete cytogenetic response (CCyR) was found to be significantly lower in patients under the 25^{th} percentile of C_{min} (1165 ng/mL). The authors also observed an association between high imatinib C_{min} and side effects such as edema (Guilhot et al., 2012).

Freeman et al. (2015) evaluated the clinical and cost effectiveness of the My5-FU assay. The authors compared the assay to gold standards of serum testing and chemotherapeutic dosing. Thirty-five studies regarding clinical effectiveness and 54 studies regarding cost effectiveness were identified. The investigators identified a high "apparent" correlation between My5-FU, high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS), although upper and lower limits of agreement ranged from -18% and 30%. Median overall survival (OS) was found to be 19.6 months for pharmacokinetic dosing (PK) compared to 14.6 months for body surface area (BSA)-guided dosing of 5-FU plus folinic acid. The authors also built a cost-effectiveness model for the My5-FU assay for metastatic colorectal cancer and head and neck cancer. The model showed My5-FU to be 100% cost effective at £20,000 per quality-adjusted life-year for both types, although the head and neck cancer was only an estimate. Despite these findings, the authors noted that "considerable uncertainties remain about evidence quality and practical implementation" (Freeman et al., 2015).

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

Macaire et al. (2019) researched the effects of TDM to optimize 5-FU chemotherapy in gastrointestinal cancer patients under and over 75 years of age. A total of 154 participants with gastrointestinal cancer participated in this study; thirty-one participants were older than 75 years of age. "At cycle 1 (C1), the 5-FU dose was calculated using patient's body surface area, then a blood sample was drawn to measure

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5-FU concentration and 5-FU dose was adjusted at the subsequent cycles based on C1 concentration. Assessments of toxicity were performed at the beginning of every cycle" (Macaire et al., 2019). Results show that approximately 71% of patients older than 75 years of age required dose adjustments after C1, while only 50% of younger patients required adjustments. Further, after dose adjustments, by cycle 3 (C3), the percentage of patients above age 75 with severe 5-FU related toxicity fell from 15% to 5%. The authors conclude that "Pharmacokinetic-guided 5-FU-dosing algorithm, leading to an improved tolerability while remaining within therapeutic concentration range, is even more valuable for patients older than 75 years than in younger patients" (Macaire et al., 2019).

Deng et al. (2020) studied the efficacy of pharmacokinetic-based 5-FU dosing management in advanced colorectal cancer patients. 153 patients with advanced colorectal cancer were randomized to receive a double-week chemotherapy with 5-FU using pharmacokinetic dosing or 5-FU chemotherapy with BSA guided dosing. In the first four weeks of treatment, patients in the experimental group were administered 5-FU according to the classic strategy of body surface area dosing before transitioning into pharmacokinetic AUC-based dosing. For the duration of the study, all patients in the control group continued with BSA guided chemotherapy. The efficacy, toxic side effects, and survival rate were assessed throughout the study. In the AUC-based dosing (experimental) group, "the rate of diarrhea significantly decreased (37.50% vs. 70.00%, P=0.010), and incidence of oral mucositis reduced (54.17% vs. 82.50%, P=0.014). Compared with the control group, the clinical benefit rate of experimental group was much higher (90.79% vs. 79.22%, P=0.046)." There was no significant difference in other 5-FU related toxic side effects such as nausea or vomiting and no difference in progression-free survival between the two groups. The authors concluded that "pharmacokinetic- based dose management of 5-Fluorouracil reduces the toxicity of chemotherapy and improves long-term efficacy of chemotherapy for advanced colorectal cancer patients" (Deng et al., 2020).

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

State and Federal Regulations, as applicable

The FDA's "Prescribing Information" documents for fluorouracil, paclitaxel, imatinib, and docetaxel do not include AUC as a method to adjust dosage (FDA, 2016a, 2016b, 2018, 2021).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) (Beumer et al., 2019)

The IATDMCT released guidelines on the dosing of 5-FU. With regards to assessing systemic exposure to 5-FU, the IATDMCT noted that area-under-curve (AUC) was the "accepted and clinically relevant" metric. They also noted that a relationship existed between 5-FU AUC and clinical activity (as well as toxicity. They go on to state, "It should be noted that statistically significant correlations between 5- FU exposure and toxicity have been observed across several disease types (squamous cell

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carcinoma of the head and neck (SCCHYN), nasopharyngeal cancer, and CRC), disease settings (metastatic, locally advanced), and dosing types (bolus, infusion)." Also, they note that "several clinical studies…have found statistically significant correlations between 5-FU exposure and clinical outcome, mostly with response rates being the metric, but also indicated by overall survival" (Beumer et al., 2019; NICE, 2014).

The IATDMCT also made remarks on the use of TDM for 5-FU. They noted that TDM reduced variability and toxicity, as well as improved clinical activity in patients receiving 5-FU, and "strongly recommend" TDM for the management of 5-FU therapy in patients with colorectal or head-and-neck cancer receiving common 5-FU regimens (Beumer et al., 2019). Concerning the use of the uracil breath test, the IATDMCT states, "The uracil breath test does not help in determining the correct does and is not recommended for clinical use" (Beumer et al., 2019).

National Comprehensive Cancer Network (NCCN) (NCCN, 2020a, 2020b, 2020c)

The NCCN published guidelines on management of antiemesis, intended to control one of chemotherapy's primary side effects. In it, the only chemotherapeutic agent listed with an AUC-based dosing regimen is carboplatin. 5-FU, docetaxel, and paclitaxel are listed as having 10-30% emetic risk whereas imatinib is listed as <30% risk. No information regarding therapeutic drug monitoring was included (NCCN, 2020a). Furthermore, the NCCN did not address TDM in either its colon cancer or head and neck cancer guidelines (NCCN, 2020b, 2020c).

National Institute for Health and Care Excellence (NICE) (NICE, 2014, 2017)

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

Clinical Pharmacogenetics Implementation Consortium (CPIC) (Amstutz et al., 2018)

In 2017, the CPIC published updated guidance on dihydropyrimidine dehydrogenase (DPYD) genotyping and fluoropyrimidine (5-FU) dosing. The following recommendations are related to TDM:
• "In DPYD poor metabolizers (DPYD-AS: 0.5 or 0), it is strongly recommended to avoid use of 5-fluorouracil containing regimens. However, if no fluoropyrimidine-free regimens are considered a suitable therapeutic option, 5-fluorouracil administration at a strongly reduced dose combined with early therapeutic drug monitoring may be considered for patients with DPYD-AS of 0.5. It should be noted, however, that no reports of the successful administration of low dose 5-fluorouracil in DPYD poor metabolizers are available to date."
• "Pharmacokinetically-guided dosing of 5-fluorouracil has been shown to result in an increase in the proportion of patients with 5-fluorouracil exposure (AUC) within the targeted therapeutic range and a reduced number of 5-fluorouracil related adverse effects. In particular, to avoid underdosing of patients with genotype-based dose reductions who tolerate higher 5-fluorouracil doses, follow-up therapeutic drug monitoring is recommended."
• For DPYD intermediate metabolizers, the following dosing recommendation was given: "Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available)."
• For DPYD poor metabolizers, the following dosing recommendation was given: "In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dosed with early therapeutic drug monitoring" (Amstutz et al., 2018).

Therapeutic Pharmacological Monitoring and Personalization of Treatments (STP-PT) Group of The French Society of Pharmacology and Therapeutics (SFPT) and the Groupe de Pharmacologie Cinique Oncologique (GPCO) (Lemaitre et al., 2018).

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The STP-PT group of the SFPT and GPCO on 5-FU therapeutic drug monitoring state that "based on the latest and most up-to-date literature data, [we] recommend the implementation of 5-FU Therapeutic Drug Monitoring in order to ensure an adequate 5-FU exposure" (Lemaitre et al., 2018).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 80299, 82542, 83789, S3722

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: Genetic Testing for 5-Fluorouracil Use in Cancer Patients

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Specialty Matched Consultant Advisory Panel 8/2019

For Policy Titled: Testing for 5-Fluorouracil Use in Cancer Patients

Medical Director review 11/2019

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Policy Implementation/Update Information

For Policy Titled: Genetic Testing for 5-Fluorouracil Use in Cancer Patients

1/1/2019 New policy developed. Genetic testing for 5 fluorouracil use in cancer patients is considered **investigational**. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

4/16/19 Revised coding table under "Billing/Coding" section. (lpr)

10/1/19 Specialty Matched Consultant Advisory Panel review 8/21/19. Deleted coding table from Billing/Coding section. No change to policy intent. Medical Director review 8/2019. (lpr)

For Policy Titled: Testing for 5-Fluorouracil Use in Cancer Patients

12/10/19 Reviewed by Avalon 3rd Quarter 2019 CAB. **Policy title changed from "Genetic Testing for 5-Fluorouracil Use in Cancer Patients" to "Testing for 5-Fluorouracil Use in Cancer Patients."** Added the following statement to "When Not Covered" section: Uracil breath tests and dihydrouracil/uracil ratio testing of plasma, serum, or urine samples *to aid in managing dose adjustment in individuals undergoing 5-fluorouracil chemotherapy are* considered **investigational.** Medical Director review 11/2019**.** (lpr)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language,

where needed. Literature review. Updated policy guidelines section and references. Deleted CPT codes 81232, 81346 and added CPT codes 80299, 82542, 83789 to Billing/Coding section. Medical Director review 10/2020. (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. No change to policy statement. (lpr)

11/16/21 Reviewed by Avalon 3rd Quarter 2021 CAB. Updated policy guidelines and references. Medical Director review 10/2021. (lpr)

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