Chemosensitivity and Chemoresistance Assays in Cancer

Guideline Number: MMG017.I
Effective Date: November 1, 2018

Table of Contents
Page

COVERAGE RATIONALE ................................................. 1
APPLICABLE CODES ................................................. 1
DESCRIPTION OF SERVICES ............................................. 1
CLINICAL EVIDENCE ................................................. 2
U.S. FOOD AND DRUG ADMINISTRATION ......................... 6
REFERENCES .......................................................... 6
GUIDELINE HISTORY/REVISION INFORMATION ................. 7
INSTRUCTIONS FOR USE ............................................. 7

COVERAGE RATIONALE

Chemosensitivity assays and chemoresistance assays are unproven and not medically necessary for predicting response to chemotherapy in individuals with cancer.

Results of the available studies fail to provide sufficient evidence that testing with chemoresistance and chemosensitivity assays leads to improved health outcomes in individuals with cancer. To date, the majority of the available studies failed to demonstrate a survival benefit with chemotherapy regimens selected based on chemosensitivity and chemoresistance assays, compared with chemotherapy regimens selected based on traditional clinical factors. Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of chemosensitivity and chemoresistance assays compared with traditional clinical factors to guide treatment selection and improve clinical outcomes including tumor response, time to progression and overall survival.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81535</td>
<td>Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination</td>
</tr>
<tr>
<td>81536</td>
<td>Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
</tr>
<tr>
<td>89240</td>
<td>Unlisted miscellaneous pathology test</td>
</tr>
</tbody>
</table>

CPT® is a registered trademark of the American Medical Association

DESCRIPTION OF SERVICES

Chemotherapy sensitivity (or "chemosensitivity") and chemotherapy resistance (or "chemoresistance") assays are intended to assist the clinician in selecting optimal chemotherapies based on tumor response in individuals with cancer. Specifically, a chemosensitivity assay refers to an in vitro laboratory analysis that assesses whether a standard
Chemotherapy drug (or more commonly, a panel of drugs), inhibits tumor growth (assay result: “drug sensitive”). In contrast, a chemoresistance assay refers to an in vitro laboratory analysis that assesses whether standard chemotherapy drug(s) do not inhibit tumor growth (assay result: “drug resistant”) (Schrag et al., 2004). Chemosensitivity and chemoresistance assays may also be collectively referred to as “chemoresponse assays.”

CLINICAL EVIDENCE

Chemosensitivity Assays
Jamal et al. (2017) conducted a retrospective analysis of 22 tumor specimens from head and neck cancer patients that had been tested with the ChemoFx assay (Precision Therapeutics, Inc.) to determine the effectiveness of a phenotypic chemoresponse assay in predicting response to chemotherapy. All specimens were confirmed as being squamous cell carcinoma. Selection of treatment was at the discretion of the treating physician and the results of the assay were not used to determine the therapy. A portion of the patients’ solid tumor was established in primary culture, then exposed to increasing doses of different chemotherapeutic agents. The resultant cell counts in the treated wells were used to indicate the tumors' response. Based on the dose response score curve, the test was scored as "responsive," "intermediate response," or "non-responsive." Of the 22 samples submitted, 16 (72.7%) showed adequate cell yield in cultures and subsequently underwent in vitro chemoresponse assays and are reported in this study, but 5 were excluded due to inadequate follow up. Of the 11 remaining patients, 9 showed a predictable chemoresponse assay (81.8% predictability of effective treatment). Three patients had a predictable good response, and 6 failed their chemotherapy regimen within 6 months of treatment and their chemoresponse assay showed an inadequate response to the agents used for treatment. At 3 years follow up, all patients who had a predictable poor response succumbed to their disease except 1, whose test showed intermediate response. The authors concluded that while the study had limitations, their findings demonstrated that chemoresponse assays may be useful adjuncts in the guiding the selection of chemotherapeutic agents in patients with head and neck cancer. Further research is required.

Ahn and colleagues (2017) performed an analysis to compare chemosensitivity by using the 21-gene recurrence score (RS) to predict the clinical benefit of chemotherapy for individuals with ER-positive/HER2-negative breast cancer. Among the patients with Oncotype Dx assay, 63 patients were identified who had chemotherapy response assays to doxorubicin based on adenosine triphosphate. The degree of chemosensitivity to doxorubicin was translated into the cell death rate (CDR). The RS was also dichotomized with a cutoff of 26. Of the 63 patients, 34 (54%), 17 (27%), and 12 patients (19%) had a low, intermediate, and high, respectively. The mean CDR differed significantly according to categorized RS, with 17.3±10.8 in the low RS group vs. 23.6±16.3 in the intermediate RS group vs. 28.8±12.6 in the high RS group. The mean CDR was significantly higher in the higher RS (26≥) group compared with the lower RS (<26) group, as well as in the high RS (>30) group compared with the low RS (<18) group. Also, continuous RS and CDR correlated positively. High RS demonstrated the odds ratio (OR = 26.33; 95% CI = 1.69-410.0) for predicting tumors with chemosensitivity on the multivariate analysis. The authors concluded that the chemosensitivity measured by in vitro chemoresponse assay was different according to the RS, with their findings also supporting that tumors with high RS has the chemosensitivity even though they are luminal/HER2-negative tumors.

A Hayes Health Technology Brief identified 7 studies including 2 prospective studies (262-276 evaluable patients of 335-462 enrolled) and 5 retrospective studies (18-304 patients) that met the selection criteria and that evaluated the efficacy of the ChemoFx assay for predicting ovarian tumor response to individualized chemotherapy regimens. Tumors were characterized as sensitive, intermediate, or resistant to each drug. Two studies compared outcomes of patients with intermediate tumor sensitivity with patients with chemosensitive tumors; 2 studies compared the outcomes of patients with tumors of intermediate sensitivity with those of patients with chemoresistant tumors. One simulation study conducted 3 analyses of assay findings from an earlier study. All of the studies, conducted and/or supported in part by Precision Therapeutics Inc., the manufacturer of ChemoFx, demonstrated more favorable outcomes, including longer progression-free survival (PFS) and overall survival (OS), in patients treated with agents to which their tumors were chemosensitive. While the available evidence suggests that there are some associations between results of the ChemoFx test and improved survival in patients with primary or recurrent ovarian cancer, due to weaknesses in study design and execution, there is insufficient proof that use of this test improves clinical decision making and outcomes compared with traditional methods of treatment selection. Additional studies with a prospective, randomized controlled design are needed to determine whether the ChemoFx assay can be used to individualize chemotherapy regimens that are more effective than standard regimens and whether use of the assay improves long-term health outcomes. (October 2014; updated August 2016)

In 2004, Samson et al. conducted a systematic review (published by the Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC]) to evaluate cancer treatments guided by chemotherapy sensitivity and resistance assays compared with empiric chemotherapy, with an emphasis on survival outcomes. This review included 10 studies and 1 retrospective study using 7 different assays. Higher response rates were observed in most studies for assay-guided patients, compared with those treated empirically, though differences were not always statistically significant. Two studies found significantly better survival rates for assay-guided therapy, but all other studies either did not provide survival data or found no significant between-group differences. Only 2 studies used randomized group
assignment. No differences were observed on tumor response or survival in 1 randomized trial. The other randomized trial reported that the assay-guided group had a higher partial response (PR) rate, but survival results were difficult to assess because the trial design had a cross-over component. Six nonrandomized studies failed to make comparisons between groups on baseline patient characteristics. Study results showed that although higher response rates for assay-guided therapy have been observed, the differences may be attributable to bias or confounding. In addition, study outcomes did not always include clinically relevant outcomes, such as patient survival. Study authors concluded that the relative effectiveness of assay-guided treatment and empiric treatment have not been established.

Tanigawa et al (2016) conducted a multicenter exploratory phase II trial to see whether a chemosensitivity test, the collagen gel droplet embedded culture drug sensitivity test (CD-DST), can adequately select patients with gastric cancer for postoperative adjuvant chemotherapy. The CD-DST using 4 different concentrations of 5-fluorouracil (5FU) was conducted with resected specimens from preregistered patients who underwent gastrectomy with D2 or more extensive lymphadenectomy. Patients who were histopathologically confirmed to have stage II or greater disease without distant metastasis were eligible for final enrollment. All patients underwent protocol specified adjuvant chemotherapy with S-1. Three-year relapse-free survival was compared between patients determined as sensitive by the CD-DST (responders) and those deemed insensitive (nonresponders). Of the 311 patients enrolled, 14 were ineligible and 27 failed to start the protocol treatment. The CD-DST failed in 64 other patients, and survival analyses were conducted with the remaining 206 patients (39 stage II disease, 155 stage III disease, and 12 stage IV disease). The outcome of patients who were determined to be responders was significantly superior to that of nonresponders regardless of the 5FU concentrations, although no differences in clinicopathologic characteristics were observed between the 2 groups, except for age. The authors concluded that the CD-DST identified those who benefit from adjuvant chemotherapy, although it deserves further evaluation in the setting of a prospective randomized trial.

Davidson et al. conducted an analysis of primary tumor samples from 159 women with endometrioid endometrial cancer (ECC) to evaluate associations between tumor grade and in vitro chemoresponse. The study group consisted of 28 individuals with grade 1 (18%), 52 with grade 2 (32%), and 79 (50%) with grade 3 tumors. The age range of participants was 31-92 years. Results were classified as sensitive (S), intermediate (I), or resistant (R) to each drug tested. Correlations between tumor grade and response were examined. Most patients (64%) had advanced disease (stage III and IV). Overall chemosensitivity was similar across all grades. “S” results to at least 1 agent were seen in 50%, 56% and 51% for grade 1, 2, and 3 tumors, respectively. There was no association between grade and in vitro response to chemotherapeutic agents except a marginal association between grade and doxorubicin response. Grade 1 and 2 disease was more likely to demonstrate “R” results for doxorubicin compared to grade 3 (G1: 19% vs G2: 25% vs G3: 8%). The authors concluded that grades 1-3 ECC have similar in vitro chemoresponse. These findings suggest that chemotherapy may be useful in advanced low grade ECCs, but further studies are needed (2016).

D’Arcangelo et al (2015) studied drug resistance and sensitivity of cancer stem cells to determine whether cancer stem cells isolation and in vitro sensitivity assay are feasible in a clinical setting. The cancer stem cells were isolated from effusions or fresh cancer tissue of 23 patients who progressed after standard therapy failure, extracted from liver metastases in 6 cases (25%), lung nodules in 2 (8%), lymph node metastases in 3 (12.5%) and pleural/peritoneal/pericardial effusion in 13 (54%). The cells were exposed in vitro to chemotherapeutic and targeted agents with successful isolation in 15 patients (63%), including 14 with lung cancer (93.3%). A sensitivity assay was successfully performed in 7 patients (30.4%), with a median of 15 drugs/combinations tested (range 5-28) and a median time required for results of 51 days (range 37-95). The authors concluded that the approach used for the STELLA trial allowed isolation of cancer stem cells in a consistent proportion of patients. The low percentage of cases completing the full procedure and the long median time for obtaining results highlights the need for a more efficient procedure.

Rogalińska et al (2015) examined an in vitro system to determine the response of mononuclear blood cells from individuals with chronic lymphocytic leukemia (CLL) with the goal of improving the efficacy of therapeutic options in these patients. The study combined 4 approaches (i.e., cell viability, apoptosis rate, differential scanning calorimetry (DSC), and immunoblotting) to develop personalized therapy protocols based on the cell sensitivity to drug exposure. The complementary analyses were performed on 28 peripheral blood samples from previously untreated CLL patients before therapy. The induction and progression of apoptosis in CLL cells exposed in vitro to purine analogs combined with mafosfamide, i.e., cladribine + mafosfamide (CM) and fludarabine + mafosfamide (FM) were assessed using the above approaches. The changes in thermal profiles (decrease/loss of transition at 95±5°C) coincided with an accumulation of apoptotic cells, a decrease in the number of viable cells, and differences in the expression of the apoptosis-related protein PARP-1. No significant changes were observed in the thermal profiles of nuclei isolated from CLL cells resistant to the treatment. The complementary assays revealed a strong relationship between both the in vitro sensitivity of leukemia cells to drugs and the clinical response of the patients, determined usually after the sixth course of treatment (after ~6 months of therapy). The authors conclusion suggests that in vitro incubations of leukemia cells with anticancer drugs is of predictive value and would help to select the optimal therapeutic strategy for individual patient in order to avoid ineffective treatment.
Cree et al. (2007) randomized 180 patients with platinum-resistant recurrent ovarian cancer to assay-directed therapy (n=94) or physician's-choice chemotherapy (n=86). Median follow-up at analysis was 18 months. Response was assessable in 147 patients: 31.5% achieved a partial or complete response in the physician's choice group compared with 40.5% in the assay-directed group (26 versus 31% by intention-to-treat analysis respectively). Intention-to-treat analysis showed a median PFS of 93 days in the physician's-choice group and 104 days in the assay-directed group (hazard ratio [HR] 0.8; 95% confidence interval [CI] 0.59-1.10, not significant [NS]). No difference was seen in OS between the groups, although 12/39 (41%) of patients who crossed over from the physician's choice arm obtained a response. Increased use of combination therapy was seen in the physician's-choice arm during the study as a result of the observed effects of assay-directed therapy in patients. Patients entering the physician's-choice arm of the study during the first year did significantly worse than those who entered in the subsequent years (HR, 0.44). The authors concluded that this small RCT has documented a trend towards improved response and PFS for assay-directed treatment. Chemosensitivity testing might provide useful information in some patients with ovarian cancer, although a larger trial is required to confirm this. The ATP-based tumor chemosensitivity assay remains an investigational method in this condition.

Wu et al. (2008) retrospectively reviewed and analyzed results of 353 consecutive patients with gastric cancer treated with MTT-directed chemotherapy (n=157) or physician's empirical chemotherapy (n=196). The survival rate of the MSG group was 47.5% and of the CG group 45.1%. No statistically significant difference in survival between the 2 groups was observed.

Two studies conducted correlational analyses of the MiCK assay for cancer patients. First, Strickland et al. (2013) evaluated the use of the MiCK assay in 109 patients with untreated acute myeloid leukemia (AML) to determine if use of the assay significantly predicted outcomes after standard AML induction therapy. Chemotherapy-induced apoptosis measured by the MiCK assay showed significant correlation with health outcomes and may be predictive of complete remission and overall survival for patients receiving standard induction chemotherapy. However, the study did not assess how disease management changes following use of the test and if important health outcomes, such as OS or PFS, improved.

Second, in a prospective blinded trial, Salom and colleagues (2012) examined if use of the MiCK assay could predict the best therapy for patients with ovarian cancer (n=104). The MiCK assay was performed prior to therapy, but treating physicians were blinded to assay results, and they selected treatment based on clinical criteria alone. Health outcomes, such as treatment response, time-to-relapse, and survival, were compared with drug-induced apoptosis as observed by the MiCK assay. Study results showed that OS in chemotherapy-naïve patients with stage III or IV disease was significantly longer if patients received a course of chemotherapy based on results of the MiCK assay, compared with shorter survival in patients who received a chemotherapy based on clinical criteria (P < 0.01; HR, 0.23). Multivariate model risk ratio showed that the use of the best chemotherapy in the MiCK assay was the strongest predictor of OS (P<0.01) in stage III or IV patients. Response rates were significantly higher if physicians used an active chemotherapy based on the MiCK assay (P=0.03). Study authors concluded that although these preliminary findings show that the MiCK assay may predict the chemotherapy associated with better outcomes in patients with ovarian cancer, future prospective RCTs are needed to ascertain these results.

**Chemoresistance Assays**

Howard et al. (2017) conducted a prospective study evaluating the use of the ChemoID drug response assay in glioblastoma (GBM) patients treated with standard of care. Forty-one patients (mean age 54 years, 59% male), all eligible for a surgical biopsy, were enrolled in an Institutional Review Board–approved protocol, and fresh tissue samples were collected for drug sensitivity testing. Patients were all treated with standard-of-care temozolomide (TMZ) plus radiation with or without maximal surgery, depending on the status of the disease. Patients were prospectively monitored for tumor response, time to recurrence, PFS, and OS. Odds ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes were estimated for cancer stem cells (CSC), bulk tumor, and combined assay responses for the standard-of-care TMZ treatment; sensitivities/specificities, areas under the curve (AUCs), and risk reclassification components were examined. Median follow-up was 8 months (range 3-49 months). For every 5% increase in in vitro CSC cell kill by TMZ, 12-month patient response (nonrecurrence of cancer) increased two-fold, OR = 2.2 (P = .016). Similar but somewhat less supported associations with the bulk tumor test were seen, OR = 2.75 (P = .07) for each 5% bulk tumor cell kill by TMZ. Combining CSC and bulk tumor assay results in a single model yielded a statistically supported CSC association, OR = 2.36 (P = .036), but a much attenuated remaining bulk tumor association, OR = 1.46 (P = .472). AUCs and [sensitivity/specificity] at optimal outpoints (>40% CSC cell kill and >55% bulk tumor cell kill) were AUC = 0.989 [sensitivity = 100/specificity = 97], 0.972 [100/89], and 0.989 [100/97] for the CSC only, bulk tumor only, and combined models, respectively. Median recurrence time was 20 months for patients with a positive (>40% cell kill) CSC test versus only 3 months for those with a negative CSC test, whereas median recurrence time was 13 months versus 4 months for patients with a positive (>55% cell kill) bulk test versus negative. Similar favorable results for the CSC test were observed for PFS and OS outcomes. Panel results across 14 potential other treatments indicated that 34/41 (83%) potentially more optimal alternative therapies may have been chosen using CSC results, whereas 27/41 (66%) alternative therapies may have been chosen using bulk tumor results. The
authors concluded that this prospective study showed statistically significant improved response rate (2.2-fold increase) in patients who were given assay-directed chemotherapy. Larger trials will potentially provide additional statistical proof of assay-directed therapy versus empirical physician choice to determine the validity of ChemoID drug response assay directed toward CSCs, which contribute to tumor propagation, maintenance, and treatment resistance.

Peterse et al. (2016) studied expression of mediators of IGF1R signaling and phosphorylation status of IRS1 in chondrosarcoma cell lines by qRT-PCR and Western blot. A total of 10 chondrosarcoma cell lines were treated with OSI-906 (IGF1R and IR dual inhibitor) after which cell proliferation and migration were determined by a viability assay and the xCELLigence system, respectively. In addition, 4 chondrosarcoma cell lines were treated with a combination of doxorubicin and OSI-906. By immunohistochemistry treatment with IGF1R/IR inhibitors did not impact proliferation or migration in any of the chondrosarcoma cell lines, even upon stimulation with IGF1. Although synergistic effects of IGF1R/IR inhibition with doxorubicin have been described for other cancers, the findings demonstrated that this was not the case for chondrosarcoma. In addition, the study detected minimal IGF1R expression in primary tumors in contrast to the high expression detected in chondrosarcoma cell lines, even if both were derived from the same tumor which suggests in-vitro culturing up-regulated IGF1R expression. The authors concluded that the IGF pathway is not expected to be an effective therapeutic marker for chondrosarcoma of bone as IGF1R is only minimally expressed in primary tumors.

Sumiyashi et al. (2016) examined the expression and role of STAT5b in human pancreatic ductal adenocarcinoma (PDAC) cell lines. Expressions of STAT5b mRNA and protein were detected in 8 kinds of pancreatic cancer cells. STAT5b shRNA clones in PANC-1 cells, which express relatively high levels of STAT5b, exhibited reduced chemoresistance against gemcitabine, adhesion and invasion compared to sham. Conversely, AsPC-1 and BxPC3 cells, which express relatively low levels of STAT5b, exhibited reduced chemoresistance compared to PANC-1 cells. Moreover, STAT5b overexpression clones in AsPC-1 cells exhibited increased chemoresistance compared to sham. STAT5b shRNA clones in PANC-1 cells were more sensitive to the proapoptotic actions of gemcitabine, as evidenced by PARP and cleaved caspase-3 activation. Gemcitabine also significantly reduced Bcl-xL levels in the STAT5b shRNA-expressing cells. While a significant correlation between STAT5b expression and overall survival rates was not observed, a significant correlation with main pancreatic duct invasion was observed. The authors’ findings suggest that targeting STAT5b in PDAC may enhance the effectiveness of other therapeutic modalities by enhancing gemcitabine chemosensitivity, increasing apoptosis and suppressing cellular adhesion and invasion.

Cloven et al. (2004) reported the results of extreme drug resistance testing to epithelial ovarian cancer (n= 5195) and found extreme drug resistance to cisplatin (10%), carboplatin (16%), cyclophosphamide (16%), doxorubicin (40%), gemcitabine (21%), paclitaxel (22%), and topotecan (13%). Researchers noted there were significant differences in the frequencies of extreme drug resistance to chemotherapeutic agents and biomarker expression among the histologic subtypes. They concluded that this data may serve as a guide to stratifying patients as they enter into clinical trials based on histology and biomarker expressions; however, patient survival benefits associated in vitro selected treatment have not been established.

d’Amato et al. (2006) reported extreme drug resistance or initial drug resistance (IDR) to non-small cell lung cancer specimens (n=3,042) to carboplatin (68%), cisplatin (63%), doxorubicin (75%), etoposide (63%), gemcitabine (72%), navelbine (42%), paclitaxel (40%), taxotere (52%), and topotecan (31%). In a follow-up study, d’Amato et al. (2007) reported resistance to multiple-agent chemotherapy to non-small cell lung cancer specimens (n=4571) to carboplatin-paclitaxel (30 %), cisplatin- navelbine (24 %), cisplatin-gemcitabine (42 %), and cisplatin-docetaxel (27 %).

There are multiple open clinical trials studying drug response assays and cancer. For more information, please go to www.clinicaltrials.gov.

Professional Societies

American Society of Clinical Oncology (ASCO)

A 2011 clinical practice guideline update states that the use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of a clinical trial setting. (Burstein et al., 2011; NCCN, 2018)

National Comprehensive Cancer Network (NCCN)

The NCCN Practice Guidelines in Oncology for Ovarian Cancer state that chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard of care chemotherapy. The NCCN panel also stated that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease should not be recommended due to lack of demonstrated efficacy (2018).
Chemosensitivity and Chemoresistance Assays in Cancer


Chemosensitivity and Chemoresistance Assays in Cancer


References


References
GUIDELINE HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/2018</td>
<td>• Updated policy header to reflect the most current UnitedHealthcare West branding; modified list of applicable products to encompass new benefit plans effective Jan. 1, 2019</td>
</tr>
</tbody>
</table>
|            | • Reorganized policy template:  
|            |   o Simplified and relocated Instructions for Use  
|            |   o Removed Benefit Considerations section  
|            | • Updated coverage rationale; modified language to clarify the listed services are unproven and not medically necessary  
|            | • Archived previous policy version MMG017.H                                                                                                         |

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member’s benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.