CHEMOSENSITIVITY AND CHEMORESISTANCE ASSAYS IN CANCER

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy 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. The MCG™ Care 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Chemosensitivity assays and chemoresistance assays are unproven and not medically necessary for predicting response to chemotherapy in patients 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 patients with cancer. To date, the majority of the available studies failed to demonstrate a survival benefit with chemotherapy regimens selected based on
Chemoresistance assays compared with 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.

CLINICAL EVIDENCE

Chemosensitivity and Chemoresistance Assays

Health Technology Assessments

A Hayes Health Technology Brief identified 7 studies including 2 prospective studies (262 to 276 evaluable patients of 335 to 462 enrolled) and 5 retrospective studies (18 to 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 the ChemoFx assay, 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 2015).

Systematic Reviews

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 two studies used randomized group assignment. No differences were observed on tumor response or survival in one 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 has not been established.

**Clinical Studies**

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 progression-free survival 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 overall survival 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 randomized clinical trial has documented a trend towards improved response and progression-free survival 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 two 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 overall survival or progression-free survival, 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 overall survival (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 randomized controlled trials are needed to ascertain these results.

**Chemosensitivity Assays**

**Clinical Studies**

Mehta et al. (2001) reported the results of extreme drug resistance testing on breast tumor tissue (n=103). Extreme drug resistance assay scores (low=2; intermediate=1 for extreme drug resistance=0) were determined for each agent tested. In vitro extreme drug resistance scores for 4-hydroxycyclophosphamide (4HC) and doxorubicin were summed for patients treated with AC, or for 4HC and 5-FU for patients treated with CMF. Clinicians making treatment selections were blinded to assay results. The authors reported that median time to progression was significantly shorter for patients with extreme or intermediate in vitro resistance (n = 55, 48 months), compared with patients with low in vitro resistance, (n=41, 100 months, p=0.022). Patients demonstrating extreme to intermediate drug resistance showed poorer survival than the low resistance group (49.5 months versus not reached, median follow-up 48 months; p=0.011). Compared with extreme drug resistance scores of 4, summed extreme drug resistance scores of 0-1 and summed extreme drug resistance scores of 2-3 were associated with a relative risk of death of 3.09 (95 % confidence interval [CI], 1.05-9.06; Cox proportional hazards model, p=0.040) and 2.35 (95 % CI, 1.07-5.15; Cox proportional hazards model, p=0.033), respectively. The authors concluded that extreme drug resistance testing identified patients with individual patterns of drug resistance prior to therapy and summed extreme drug resistance scores were significantly associated with time-to-tumor progression and overall survival.
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 %).

**Professional Societies**

**American Society of Clinical Oncology (ASCO)**

A 2011 clinical practice guideline update reflects new evidence, but no change in the recommendations from the previous ASCO technology assessment (Schrag et al., 2004). The 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. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient’s health status and treatment preferences. Because the in-vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority (Burstein et al., 2011; NCCN, 2016).

**National Comprehensive Cancer Network (NCCN)**

The NCCN Practice Guidelines in Oncology for Ovarian Cancer state that while chemosensitivity/resistance and/or other biomarker assays are being used to aid in selecting chemotherapy in situations where there are several equivalent chemotherapy options available, the current level of evidence is not sufficient to replace 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 (NCCN, 2016).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Laboratories that perform in vitro chemosensitivity and chemoresistance testing are regulated by the FDA under the Clinical Laboratory Improvement Amendments (CLIA).

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not cover human tumor drug sensitivity assays as they are considered experimental. Refer to the National Coverage Determination (NCD) for Human Tumor Stem Cell Drug Sensitivity Assays (190.7).

Local Coverage Determinations (LCDs) exist; see to the LCDs for Biomarkers for Oncology, Circulating Tumor Cell Marker Assays, MolDX: MGMT Promoter Methylation Analysis, MolDX: Molecular Diagnostic Tests (MDT), Molecular Diagnostic Tests (MDT) and Molecular Pathology Procedures.

**REFERENCES**


**POLICY HISTORY/REVISION INFORMATION**

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<th>Date</th>
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<tbody>
<tr>
<td>11/01/2016</td>
<td>- Updated list of applicable CPT codes; removed 81287</td>
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<td>- Updated supporting information to reflect the most current clinical evidence</td>
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