CHEMOSENSITIVITY AND CHEMORESISTANCE ASSAYS IN CANCER

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Related Policies:
Gene Expression Tests

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit 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

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 (such as maternity benefits), 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 guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage.

COVERAGE RATIONALE

Chemoresistance assays and chemosensitivity assays (including, but not limited to, the ChemoFx® assay) are unproven and not medically necessary for predicting response to chemotherapy.
Results of the available studies fail to provide convincing evidence that information obtained with chemoresistance and chemosensitivity testing is beneficial for health outcomes in patients with cancer. Although numerous studies have been conducted, the evidence does not demonstrate that there is an improved survival among patients in whom chemosensitivity and chemoresistance assays were used to select chemotherapy regimens. Well-designed prospective, randomized controlled clinical trials are needed to determine the impact of chemosensitivity and chemoresistance assays on tumor response and patient survival.

APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit 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 claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

CPT® Code	Description
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
86849	Unlisted immunology procedure
89240	Unlisted miscellaneous pathology test

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DESCRIPTION OF SERVICES

Chemotherapy sensitivity and resistance assays offer the potential of selecting cancer treatments based on responsiveness of individual tumors. The goal is to select a drug or combination of drugs to which a tumor is most sensitive, and to avoid drugs to which the tumor is resistant. A chemotherapy sensitivity assay refers to any in vitro laboratory analysis that tests whether tumor growth is inhibited by a known chemotherapy drug or, more commonly, a panel of drugs. An example of a chemosensitivity assay is the ChemoFx® assay by Precision Therapeutics, Inc. Sometimes these assays are referred to as chemoresistance assays because they identify potentially ineffective drugs that do not influence in vitro tumor cell growth (Schrag et al., 2004).

CLINICAL EVIDENCE

Chemosensitivity Assays

A Hayes Health Technology Brief identified five uncontrolled studies that evaluated the efficacy of the ChemoFx assay for predicting tumor response. None of these studies provided a systematic, prospective analysis of the efficacy of chemotherapy selected by traditional methods versus chemotherapy directed by results of the ChemoFx assay. All of the available studies were conducted and/or supported in part by Precision Therapeutics Inc., who developed the ChemoFx assay (Ness et al., 2002; Gallion et al., 2006; Mi et al., 2008; Herzog et al., 2010; Huh et al., 2011). The limited evidence is insufficient to prove that the ChemoFx assay improves clinical decision making and patient outcomes compared with traditional methods of treatment selection. Additional studies with a prospective, randomized and controlled design are needed to determine whether information from the ChemoFx assay can provide any benefit to patients and to demonstrate that long-term patient outcomes improve when individualized regimens are used instead of the standard regimens (Hayes, 2011; updated 2012).

Cortazar and Johnson (1999) conducted a literature review including 12 studies to determine the potential efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing (DST) compared to empiric regimens for patients with cancer. Five hundred six patients (33%) were treated with chemotherapy that was selected with the use of in vitro DST. The mean response rate for patients treated with in vitro-selected therapy was 27% (range, 10% to 100%; n = 12 studies) compared with 18% (range, 0% to 100%; n = 7 studies) for patients treated with empiric therapy. Five studies (only one randomized) evaluated the impact of chemotherapy selected by in vitro DST on patient survival. Three studies showed that survival was 1 to 4 months longer for the 238 patients treated with empiric chemotherapy compared with that of the 65 patients treated with chemotherapy that was selected by in vitro testing. Two nonrandomized studies showed that survival was 4 or 19 months longer for 27 patients treated with chemotherapy selected by in vitro testing compared with that of 80 patients who were treated with empiric chemotherapy. The authors concluded that only one-third of the patients (n=1545) entered in these 12 prospective studies of in vitro DST were actually treated with an in vitro best regimen. The response rates seem to be better with in vitro selected chemotherapy regimens than with empiric regimens, but the impact on survival has not been adequately addressed.

A meta-analysis by Von Hoff (1990) of 54 retrospective studies (n=2,300) reported a positive predictive value of only 69% and a negative predictive value of 91%.

In 2004, Samson et al. (from the Blue Cross and Blue Shield Association Technology Evaluation Center) published a systematic review of the evidence comparing therapy guided by chemotherapy sensitivity and resistance assays with empiric chemotherapy, emphasizing survival outcomes. This review included 10 studies (Cortazar, 1997; Kurbacher, 1998; Maenpaa, 1995; Shaw, 1996; Shaw, 1993; Von Hoff, 1983; Von Hoff, 1991; Von Hoff, 1990; Wilbur, 1992; Xu, 1999) and one retrospective study (Loizzi, 2003) using seven 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 (Cortazar, 1997; Loizzi, 2003), but all other studies either did not provide survival data or found no between-group differences. Only two studies used random assignment of patients to groups. No differences were observed on tumor response or survival in one randomized trial (Maenpaa, 1995). The other randomized trial reported that the assay-guided group had a higher partial response (PR) rate, but it is difficult to assess survival results because the trial design had a cross-over component (Von Hoff, 1990). Six nonrandomized studies failed to make comparisons between groups on baseline patient characteristics (Von Hoff, 1983; Von Hoff, 1991; Shaw, 1996; Shaw, 1993; Wilbur, 1992; Cortazar, 1997). The authors concluded while higher response rates for assay-guided therapy have been observed, differences may be attributable to bias or confounding. Little evidence on survival is available. These results do not establish the relative effectiveness of assay-guided treatment and empiric treatment. Randomized trials are needed.

Ugurel et al. (2006) conducted a multicenter phase II trial to investigate the efficacy of a sensitivity-directed, first-line chemotherapy using an ATP-based luminescence viability assay in metastasized melanoma patients. The per protocol population could be divided into 22 (42%) chemosensitive and 31 (58%) chemoresistant patients by an arbitrary chemosensitivity index. Objective response was 36.4% in chemosensitive patients compared with 16.1% in chemoresistant patients; progression arrest was 59.1% versus 22.6%. Chemosensitive patients showed an increased overall survival of 14.6 months compared with 7.4 months in chemoresistant patients.

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 0.8, 95% confidence interval 0.59-1.10, not significant). 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 (hazard ratio 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.

The clinical evidence was reviewed on May 21, 2013 with no additional information identified that would change the unproven conclusion.

Chemoresistance Assays
Note: According to a June 2010 press release by Exiqon, Oncotech is no longer in business.

Mehta, et al. (2001) reported the results of extreme drug resistance testing on breast tumor tissue (n = 103). Extreme drug resistance assay scores of 2 for low, 1 for intermediate, or 0 for extreme drug resistance 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. Treatment selection was 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 to 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 to 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 %, 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 that summed extreme drug resistance scores were significantly associated with time to tumor progression and overall survival.

Haroun, et al. (2002) described a drug resistance profile (extreme, intermediate, or low) based on statistical comparison to a historical database of brain tumor specimens tested against the same panel of chemotherapeutic agents. The authors stated that through continued analysis and compilation of data from multiple institutions, chemoresistance profiles could assist future investigators with the development of rationale clinical trials and treatment regimens for patients with brain tumors.

In a retrospective study of extreme drug resistance testing on newly diagnosed advanced ovarian cancer patients, Holloway, et al. (2002) stated that patients with ovarian tumors demonstrating in vitro drug resistance to platinum were at significantly increased risk for progression and death when treated with standard platinum-based regimens. Median progression free survival was six months for tumors exhibiting extreme resistance to platinum (n = 17) compared to 24 months for tumors exhibiting low resistance to platinum (n = 62).

Cloven, et al. (2004) reported the results of extreme drug resistance testing to epithelial ovarian cancer (n = 5,195) and found extreme drug resistance to cisplatin (10 %), carboplatin (16 %), cyclophosphamide (16 %), doxorubicin (40 %), gemcitabine (21 %), paclitaxel (22 %), and topotecan (13 %). The 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 be able to serve as a guide to stratifying patients as they enter into clinical trials based on histology and biomarker expressions while patient survival benefits with in vitro selected treatment remain unproven.

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 = 4,571) to carboplatin-paclitaxel (30 %), cisplatin- navelbline (24 %), cisplatin-gemcitabine (42 %), and cisplatin-docetaxel (27 %).

The clinical evidence was reviewed on May 21, 2013 with no additional information identified that would change the unproven conclusion.

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 2004 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 the 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).

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. This is a category 3 recommendation (based on any level of evidence but reflects major disagreement). 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, 2013).

The clinical evidence was reviewed in April 2014 with no additional information identified that would change the unproven conclusion.

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. See the following web site for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. Accessed April 19, 2014

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 Assay (190.7). Accessed April 19, 2014

Local Coverage Determinations (LCDs) exist for human tumor drug sensitivity assays. Refer to the LCDs for Circulating Tumor Cell Marker Assays, Molecular Diagnostic Tests (MDT) MyPRS Genetic Expression Profile Testing, In Vitro Chemosensitivity & Chemoresistance Assays and Noncovered Services. Accessed April 19, 2014

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
09/01/2014	• Reorganized policy content • Added benefit considerations language for *Essential Health Benefits for Individual and Small Group* plans to indicate: o 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") o 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 (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans o The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage • Updated coverage rationale; added language to indicate the unproven services are "not medically necessary" • Updated list of applicable CPT codes; added 81287 • Archived previous policy version 2013T0533E