



CIGNA MEDICAL COVERAGE POLICY

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**Subject Tumor In Vitro
Chemosensitivity and
Chemoresistance Assays**

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Coverage Policy

CIGNA does not cover in vitro chemoresistance or chemosensitivity assays because such testing is considered experimental, investigational or unproven.

General Background

The goals of chemotherapy treatment are to utilize the most effective agents for killing tumors or cancer-cells, while avoiding patient toxicity. Various factors are taken into consideration when choosing a chemotherapy regimen including the type of cancer, stage of cancer, other medical conditions of the individual, concomitant drug therapies, and previous chemotherapy. Clinical assessment, imaging techniques, and surgical staging are considered the standards of care for identifying response to therapy.

In vitro chemotherapy sensitivity and resistance assays (CSRAs) have been proposed as methods for determining response and for customizing cancer therapies for individuals. The underlying hypothesis for in vitro assays is that the drug response profile for an individual patient will undoubtedly differ based on their intrinsic genetic diversity and the development of tumor subclones (Harry, 2009). In vitro testing involves subjecting a sample of tumor cells to specific chemotherapeutic agents in the laboratory, usually involving isolated tissue, organs, or cell preparations. By determining the cellular response to these agents, it is hypothesized that individualized treatment protocols may be planned.

The goals of in vitro chemosensitivity assays are to assist with the selection of chemotherapy drugs for the treatment of cancer in individuals based on the response of each patient's tumor cells to a specific chemotherapeutic agent(s). Tumor cells are obtained from the individual with cancer, cultured in the laboratory, and exposed to specific a specific drug or battery of drugs over a period of time. If they can demonstrate excellent predictability these assays could potentially be helpful in patients with curable diseases and allow for the identification of the rare patient with primary resistant disease.

In vitro chemoresistance assays are used to deselect or predict those chemotherapy drugs that are non-responsive to a specific tumor. During the assay, tumor cells are cultured and exposed to concentrations of selected chemotherapeutic agents over a prolonged period of time. Tumors are reported as having high, intermediate or low drug resistance, with the assumption being that drugs with low resistance may be effective in vivo (i.e., within the body), while high-resistance drugs may be less effective. According to Harry et al., (2009) the accuracy of in vitro testing in identifying clinical drug resistance is 90%, with a 70% positive predictive value.

Limitations of Chemosensitivity and Resistance Assays (CRSAs): The use of in vitro assays to detect chemosensitivity or resistance has not yet translated into routine clinical practice. The ability of these tests to identify active and inactive chemotherapy agents in the laboratory setting does not necessarily translate into an accurate and clinically useful prediction of patient response to therapy and patient survival (Harry, 2009).

A major limitation of CSRAs stems from the need to use in vitro cell culture. The genetic variations suited to survival in culture may yield an altered phenotype. Additionally, the immune system is known to interact with, and in some instances alter, the growth of tumor (Ferriss, 2010). In vitro sensitivity or resistance to an agent does not ensure in vivo (i.e., testing on a living organism) response because of a variety of host factors, including drug concentration within the body, vascularity to the tumor or the presence of pharmacologic sanctuaries, such as the blood-brain barrier, and detoxification of the drug within the body. Additionally, tumor growth in vitro may not mirror tumor growth in vivo, nor can it be established that the biopsy tissue used in the assays is truly representative of the entire tumor. Other limitations of in vitro assays include the need for complex labor intensive laboratory work, the generally low yield of assays and the prolonged time required for results which limits the ability to allow for early prediction of therapy response (Harry, 2009).

Data are limited regarding methods of predicting cellular drug sensitivity and resistance. The precise pathway of cell death is difficult to determine. Apoptosis (i.e., cell death) is dependent on several factors, including tumor cell type and volume, the drug combinations being used and the doses that are being prescribed. Some tumor cell components provide protection of the cancer cell against chemolytic agents and act as transporters moving the drugs away from the tumor cells.

According to Schrag et al. (2004), the chemotherapy combination that often looks most promising on the basis of the CSRA is the same one that would have been chosen in the absence of assay results. If the assay rarely alters the recommended treatment strategy, and results consistently serve to validate the use of the same therapies that would be selected on the basis of the clinical trial literature, utility is limited.

At present, published studies in the peer-reviewed scientific literature are limited by small numbers, lack of prospective studies, no randomization, and the availability of newer chemotherapeutic agents since the advent of these studies. There is also a lack of prospective randomized studies comparing response rates or disease-free survival of patients receiving assay-assisted therapy with those receiving empirical therapy (i.e., choice of treatment based on current evidence of patient outcome) (Harry, 2009).

Testing Methods: In vitro testing has not yet gained widespread acceptance, and there is continued debate concerning its optimal clinical applicability (Harry, 2009). Randomized controlled clinical trial data are lacking regarding improved survival outcomes in patients for whom chemotherapy is directed by in vitro chemosensitivity or chemoresistance assay results.

While varying techniques may be used during processing, each test involves the same basic steps of tumor sampling and cell isolation, establishment of cell culture, incubation of cells with chemolytic agents, analysis of results and verification of positive and negative controls (Ferriss, 2010).

CSRA test methods include (this list may not be all-inclusive): extreme drug resistance assays (e.g., Oncotech EDR[®] Assay, Exiqon, Inc., Tustin, CA), 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H tetrazolium bromide

(MTS/MTT) assay, thymidine incorporation assays (e.g., ChemoFX Assay[®], Precision Therapeutics, Inc., Pittsburgh, PA), microculture kinetic assays of apoptosis (e.g., MiCK[™], Diatech Oncology, Brentwood, TN), flow cytometric chemosensitivity assays (FCCA), and adenosine triphosphate (ATP) assays. Other assays include, fluorescence (cytoprint) assays, differential staining cytotoxicity assays (e.g., Oncotech DiSC[®], Exiqon, Inc., Tustin, CA), human tumor stem cell assays (HTCA), and human tumor cloning assays. Randomized clinical trial data are lacking for in vitro chemoresistance and chemosensitivity assays. Several tests are briefly described below.

Literature Review

While a trend toward increased response rates and survival has been reported in several studies for various assays, no statistically significant differences have been demonstrated in other studies, including results of a randomized controlled trial published by Cree et al. (2007). A systematic review by Samson et al. (2007) evaluated the efficacy of therapy that is guided by chemotherapy sensitivity and resistance assays compared to empiric chemotherapy, with an emphasis on patient survival outcomes. Of the eleven studies included in this review, two studies randomly assigned patients to either assay-guided treatment or empiric treatment. Although higher response rates were seen in patients with assay-guided treatment compared to patients treated with empiric therapy, outcomes were not statistically significant. These studies were limited by study design, lack of patient survival documentation or reporting of adverse event data.

Extreme Drug Resistance Assay (EDR): In this assay, human tumor cells are cultured and exposed to drugs at high concentrations for a prolonged period. Tumor cells that survive this overwhelming exposure are considered to demonstrate 'extreme drug resistance'. Prospective randomized clinical trial data demonstrating improved outcomes are lacking. At this time the clinical utility of this assay has not been established.

Matsuo et al. (2010) retrospectively evaluated the role of in vitro EDR assay to predict the response to platinum and taxane combination chemotherapy in women with advanced ovarian and uterine carcinosarcoma. Fifty-one samples were available in which EDR results were known; of these 17 women received combination chemotherapy. Clinical response to chemotherapy in the presence of EDR to at least one of the two drugs (EDR-PT) was significantly lower than non-EDR-PT (37.5% versus 100%, respectively, $p=0.009$). Sensitivity, specificity, and positive and negative predictive values for clinical response in non-EDR-PT were 75%, 100%, 100%, and 62.5%, respectively. EDR-PT showed a significantly lower one-year progression-free survival (28.6% versus 100%, respectively), and five-year overall survival (26.9% versus 57.1%, respectively).

Karam et al. (2009) conducted a retrospective review of EDR assay and clinical outcomes from 377 individuals with epithelial ovarian cancer who had an assay performed at the time of their primary or subsequent cytoreductive surgeries. EDR assay failed to independently predict or alter outcomes in individuals treated with current standards of primary cytoreductive surgery followed by platinum and taxane combination chemotherapy.

Cloven et al. (2004) reported the retrospective serial results of 5195 epithelial ovarian cancers that were studied to determine whether any relationship existed between histological subtypes and chemoresistance. The EDR[®] assay was used to determine the responsiveness of each subset during exposure to standard chemotherapeutic agents. Although there were significant differences in the frequencies of response and biomarker expression among the histologic subtypes, patient survival benefits with in vitro selected treatment remain unproven.

Loizzi et al. (2003) reported the results of a retrospective study of 50 women with recurrent ovarian carcinoma who were treated with a chemotherapy regimen based on EDR assay guidance compared with results of a control group ($n=50$) who were treated empirically. In the platinum-sensitive group, individuals with extreme drug resistance-directed therapy had an improved response rate compared with those treated empirically (65% versus 35%, $p=.02$). Overall and progression-free survival was also improved in the EDR assay group compared with the control group ($p=.005$ overall; $p=.02$ progression-free, respectively). There was no improved outcome in the patients who underwent assay-guided therapy in the platinum-resistant group. In multivariate analysis, platinum-sensitive disease, EDR-guided therapy and early stage of disease were independent predictors for improved survival.

3-(4, 5-Dimethyl-2-Thiazolyl)-2, 5-Diphenyl-2H Tetrazolium Bromide (MTS/MTT) assay: In this chemosensitivity assay, single tumor cell suspensions are exposed to MTT. If cells are metabolically active, blue crystals are formed. Data are lacking regarding improved outcomes with the use of this test. At this time clinical utility has not been established.

Wu et al. (2008) reported no significantly different outcomes ($p=0.57$) between 353 consecutive patients with gastric cancer treated with 3-(4, 5-Dimethyl-2-Thiazolyl)-2, 5-Diphenyl-2H Tetrazolium Bromide (MTT)-directed chemotherapy ($n=157$) or physician's empirical chemotherapy ($n=196$). The overall 5-year survival rates of the MTT-sensitive group (MSG) and control group (CG) were 47.5% and 45.1%, respectively. This retrospective study suggests that the clinical benefit of the MTT chemosensitivity assay is limited.

To evaluate the predictive value of an in vitro MTT assay Jun et al. (2007) obtained bone marrow aspirates from 103 adults and children with acute leukemia at the time of initial diagnosis or relapse. Ninety study participants received induction chemotherapy. Bone marrow aspirate samples were subjected to the MTT assay to determine chemosensitivity. There was no significant correlation between the MTT assay results and disease-free survival or overall survival. Differences of mean MTT dead cell percentages between samples taken at initial diagnosis and those at relapse were not statistically significant. In vitro chemosensitivity testing with the MTT assay predicted whether those with acute myelogenous leukemia achieved remission after induction chemotherapy and remained in continuous remission or relapsed, but not in those with acute lymphoblastic leukemia.

In a retrospective review using the MTS assay, O'Toole, et al. (2003) reported on the results of a correlational study involving 88 tumor samples of individuals undergoing surgery for carcinoma of the cervix, endometrium, or ovary. In vitro sensitivity data was provided to the physician; however, the selection of chemotherapy was decided by the oncologist. In most cases standard chemotherapy regimens were given. Retrospective correlations between chemosensitivity/resistance and clinical response were available in 45 of 88 cases. The authors note that the majority of correlations were for the ovarian cancer patients. In 15 cases the tumor was found to be resistant in vitro and in 14 of these cases the patient presented with a recurrence, had evidence of active disease or died from the disease, which suggests 93% prediction accuracy for resistance. In 30 instances the tumor was sensitive to a drug in vitro. Twenty-six of these patients were free of disease at the time of study publication. The authors note that this suggests 87% prediction accuracy for sensitivity and that the probability of a negative in vitro test for a patient who failed to respond clinically was 78%. Study limitations include non-randomized and retrospective design, and assumptions regarding cause of active disease, disease progression, or death. The authors note that randomized prospective trials are needed to validate study results.

ChemoFx[®] Drug Response Assay: The ChemoFx assay adds chemotherapy drugs or drug combinations to epithelial cells isolated from an excised ovarian carcinoma. It is proposed that this assay can provide predictions of responses to specific agents alone or in combination. The level of cell kill is recorded for each drug across multiple doses. Prospective clinical trial data demonstrating improved clinical outcomes are lacking and the clinical utility of this assay has not been established. Several randomized clinical trials are ongoing.

Herzog et al. (2010) attempted to determine if there was an association between tumor responses in vitro to platinum therapy by comparing the ChemoFx[®] drug response marker and overall survival (OS) after first-line platinum-based chemotherapy in 192 individuals with advanced-stage primary ovarian cancer. One hundred and forty-seven participants were included in another clinical trial publication. Date of death was determined by an independent epidemiologist consultant, who was blinded to the ChemoFx results. The average number of different drugs or combinations ordered by the physician and tested by using ChemoFx was 8.9. The majority of tumors were tested for, and showed response to, platinum compounds. Scores were classified as responsive, intermediately responsive, or non-responsive. Patients receiving a responsive or intermediately responsive drug had significantly longer OS than patients receiving a non-responsive drug ($p=.0386$). The ChemoFx score significantly associated with OS ($p=.023$). Final treatment decisions were made by the patient's physicians. It is unknown the extent to which test results influenced clinical decision making; therefore the clinical utility of this test cannot be determined.

In a feasibility study, Mi et al. (2008) tested expanded tumor cells from biopsies of 62 breast lesions for chemoresponse using the ChemoFx assay. Pathologic complete response was determined in 34 individuals. In a limited initial patient outcome correlation, assay score of docetaxel/capecitabine significantly predicted pathologic complete response. The cross-validated model was 75% accurate.

Microculture Kinetic Assay of Apoptosis (MiCK[™]): This assay determines the extent of apoptosis, or cell death, in a population of cells after exposure to cytotoxic agents. Prospective randomized clinical trial data

comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Ballard et al. (2010) reported results of a study of 19 individuals with endometrial cancer. Tumors were analyzed with the microculture kinetic assay of apoptosis (MiCK) assay against various single and combination chemotherapy regimens to determine chemosensitivity responsiveness for 15 individuals. Assay results of study participants were compared to clinical response rates of participants of previously completed Gynecologic Oncology Group (GOG) trials. There was correlation between the demonstrated activity of the chemotherapy regimens used in vivo GOG trials and the chemosensitivity of tumor samples used for the MiCK assay ($p < 0.0328$). According to the authors, the results indicate that 25% of study participants might be treated with single agent chemotherapy selected by the MiCK assay, although this prediction is based on wide confidence intervals because of the small number of samples.

Flow Cytometric Chemosensitivity Assay (FCCA): In FCCA, cryopreserved cells are thawed, washed, re-suspended, and added to a specific chemotherapy drug or drug combinations in various drug concentrations. Prospective randomized trial data are lacking regarding improved patient outcomes. At this time the clinical utility of FCCA has not been established.

Galderis et al. (2009) studied the relationship between in vitro drug sensitivity of diagnostic leukemic blasts from 30 children with acute lymphoblastic leukemia (ALL) and the rapidity of response to induction therapy. Study participants were enrolled on Children's Oncology Group clinical trials from 1997 to 2007. Five drugs were each tested at three concentrations. The in vitro drug sensitivity of de novo leukemic blasts among various clinical subsets was also tested. Cellular drug response was determined successfully by FCCA in 30 of 38 samples analyzed. Slow early response to induction therapy was associated with a significantly increased lymphoblast survival after exposure to glucocorticoid therapy in vitro. Limitations of the study include small sample size, the lack of exposing blasts simultaneously to multiple induction drugs as occurs with in vivo treatment, and the failure to account for potential drug synergism.

Adenosine Triphosphate (ATP) Chemotherapy Response Assay: In this technique, tumor cells are isolated and subjected to multiple single drug and combination drug therapies at increasing drug concentrations. Randomized clinical trial data are lacking regarding improved clinical outcomes with the use of this assay. At this time clinical utility has not been established.

Kim et al. (2010) assessed the accuracy of ATP-CRA using clinical response as a reference standard in 48 individuals with chemo-naïve, locally advanced or metastatic gastric cancer. Thirty-six individuals had evaluable results. The chemosensitivity index method yielded an accuracy of 77.8%. Specificity, sensitivity, and negative and positive predictive values were 95.7%, 46.2%, 85.7%, and 75.9%, respectively. The in vitro chemosensitivity group showed higher response rates (85.7% versus 24.1%, $p = 0.005$) compared with the in vitro chemoresistant group.

Cree et al. (2007) conducted a prospective randomized controlled trial to determine the response rate and progression-free survival following chemotherapy in patients with ovarian cancer who had been treated according to a tumor chemosensitivity assay in comparison with physician's choice. A total of 180 patients were randomized, with 94 receiving assay-directed treatment and 86 receiving physician's choice therapy. Evidence of response was not significantly different between the two groups ($p < 0.3$). Additionally, there was no significant difference in the median progression free- or overall survival between the two groups, ($p < 0.14$ and $p < 0.8$, respectively), although there was a trend towards improved response and progression-free survival for assay-directed treatment.

Histoculture Drug Response Assay (HDRA): HDRA is a type of test evaluating cell death, or apoptosis. Tumor specimens are minced and plated in the presence of single drug or drug combinations. After histoculture, specimens are analyzed for cell death by inhibition rate. Randomized clinical trial data demonstrating improved outcomes are lacking. At this time the clinical utility of this assay has not been established.

Using the in vitro HDR chemosensitivity assay, Lee et al. (2009) attempted to determine the chemosensitivity of 65 fresh tumor samples obtained from women with cervical cancer. Inhibition rates of ten chemotherapeutic agents were tested. Although five agents were determined to be chemosensitive against these tumor samples, there were no significant differences in chemosensitivity according to histologic types or stage. Further

evaluation is warranted to confirm the relationship between results of the histoculture drug response assay (HDRA) and clinical responses. In a study analyzing results using the HDRA in a case series study involving 173 patients and 164 evaluable tumors, Nakada et al. (2004) reported a true-positive rate of 90%, true-negative of 78.9%, and overall accuracy of 82.8%.

Summary for Chemosensitivity and Chemoresistance Assays (CSRAs): Prospective randomized clinical trial data are lacking to evaluate overall survival of individuals treated with assay-directed regimens compared with controls treated with an empiric regimen. The evidence regarding CSRAs is derived from correlational trials that do not use intent-to-treat analysis or investigate survival rates. A majority of studies do not assess overall survival as a primary endpoint which limits the clinical utility of the test (Ferriss, 2010). Additionally, optimal dosing, treatment regimens, and specific patient selection criteria should be determined. Although they remain an active focus of research, data are insufficient to demonstrate an improvement of health outcomes with the use of these tests. At this time in vitro CSRAs have not been established as a standard of practice in the clinical setting.

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).

Professional Societies/Organizations

American Society of Clinical Oncology (ASCO, 2004): On behalf of the ASCO Working Group, Schrag et al. (2004) published recommendations on the use of chemotherapy sensitivity and chemoresistance assays to select chemotherapeutic agents for individual patients. According to Schrag, chemosensitivity and chemoresistance assays are “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.”

National Comprehensive Cancer Network (NCCN): Regarding ovarian cancer, the NCCN Guidelines (2010) note “in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended, owing to the lack of demonstrable efficacy for such an approach.” The Guidelines also note “Chemosensitivity/resistance assays are being used in some NCC centers 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.”

Summary

Although numerous small studies and trials have been conducted, standards have not been established for the use of tumor in vitro chemosensitivity or chemoresistant assays in clinical practice. Well-designed prospective, randomized controlled clinical trials are needed to determine the potential clinical role of assay-directed therapies and their impact on tumor response and patient survival. At this time there is insufficient evidence to demonstrate the clinical correlation between the use of these tests and improved patient health outcomes. Although an active focus of research, the clinical utility of in vitro chemoresistance and chemosensitivity assays has not been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report in vitro chemoresistance or chemosensitivity assays:

CPT [®] * Codes	Description
86849	Unlisted immunology procedure
87999	Unlisted microbiology procedure
88299	Unlisted cytogenetic study
89240	Unlisted miscellaneous pathology test

ICD-9-CM Diagnosis Codes	Description
	All codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	11/15/2007	0203	Tumor in Vitro Chemosensitivity and Chemoresistance Assays
Great-West Healthcare	2/22/2008	06.338.02	Chemosensitivity and Chemoresistance Assays, In Vitro

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