Cigna Medical Coverage Policy

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

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Coverage Policy

Cigna does not cover tumor 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. CSRAs are in vitro laboratory analyses of sample cells taken from a primary or metastatic tumor (before or after treatment with chemotherapy) to provide predictive information regarding a tumor's particular chemotherapy sensitivity or resistance (Burstein, 2011). The underlying hypothesis for in vitro assays is that the drug response profile for an individual will undoubtedly differ based on their intrinsic genetic diversity and the development of tumor subclones (Harry, 2009). By determining the cellular response to these agents, it is hypothesized that individualized treatment protocols may be planned.

Chemosensitivity Assays: The goal of in vitro chemosensitivity assays is 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 a specific drug or battery of drugs over a period of time. If these assays demonstrate excellent predictability they could potentially be helpful in treating patients with curable diseases and allow for the identification of the rare patient with primary resistant disease.

Chemoresistance Assays: 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 been 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). The precise pathway of apoptosis (i.e., cell death) is difficult to determine and 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.

A major limitation of CSRAs stems from the need to use in vitro cell culture. 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. 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). 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. 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 uncontrolled study design, small patient numbers, and the availability of newer chemotherapeutic agents since the advent of these studies. There are limited prospective randomized studies comparing response rates or disease-free survival of patients receiving assay-assisted therapy to those receiving empirical therapy (i.e., choice of treatment based on current evidence of patient outcome) (Harry, 2009). The overall effect on health outcomes is unknown.

Testing Methods: 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). Several tests are briefly described below.

CSRA test methods include (this list may not be all-inclusive): extreme drug resistance assays, 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H tetrazolium bromide (MTS/MTT) assay, drug response assay (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), adenosine triphosphate (ATP) assays, and histoculture drug resistance assays (HDRA®, Anticancer, Inc., San Diego, CA). Other assays include fluorescence (cytoprint) assays, differential staining cytotoxicity assays, human tumor stem cell assays (HTCA), and human tumor cloning assays.

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.

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 (CSRAs) 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 and reporting of adverse event data.

The American Society of Clinical Oncologists (ASCO) published a systematic review and analysis of the medical literature (2011) regarding the effectiveness of chemosensitivity and chemoresistance assays. ASCO notes that published literature was included or excluded based on the following criteria: outcome comparisons (prospective or retrospective) for patients whose chemotherapy was chosen empirically (based on clinical trial literature) as opposed to selection based on results of CSRAs; CSRA performance on viable patient tumor tissue as opposed to other forms of diagnostic testing performed on nonviable tumor tissue; a study sample size of ≥ 20 patients per arm; and primary end points of cancer events or survival including overall survival (OS) and/or response to therapy, disease-free survival, progression-free survival, local tumor control, and/or treatment toxicity. Four publications were selected for inclusion in the review. Additionally, ASCO reviewed data from several published studies involving use of the ChemoFX assay. Limitations to the studies included lack of blinding, lack of comparison groups and selection of chemotherapy at the discretion of the treating physician. Review of the literature did not identify CSRAs for which the evidence base was sufficient to support use in oncology practice. ASCO notes the use of CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting.

Extreme Drug Resistance (EDR) Assay: In this assay, human tumor cells are cultured and exposed to high concentration of drugs for a prolonged period. Tumor cells that survive this overwhelming exposure are considered to demonstrate 'extreme drug resistance'.

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).

In a nonrandomized comparison Joo et al. (2009) evaluated 78 patients with epithelial ovarian cancer, tubal cancer or primary peritoneal carcinoma, with 39 patients in the EDRA group and 39 patients in the physician's choice/empiric therapy group. There was no significant difference in overall response rate between EDRA group and the control group 84.5% vs. 71.8%, respectively, p=0.107). However, 93.8% of patients in EDRA group did not show EDR to at least one drug and its response rate was significantly higher than that of the control group (93.3% vs. 71.8%, p=0.023).

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). Outcomes were not improved for 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.

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.

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.

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.

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.

ChemoFx® Drug Response Assay: According to the manufacturer's website, ChemoFx is a drug response marker. It quantifies an individual cancer patient's probable tumor response to up to 12 various

chemotherapeutic and biologic agents—providing both sensitivity and resistance information (2009). Small tissue samples from surgery (i.e., ≥35 mg and ≤1g), two core needle biopsies (i.e., ≥35 mg), or ascites or pleural fluid (i.e., ≥100 cc) of ovarian, breast, endometrial, cervical, lung and colorectal tumor types may be tested. Cells are cultured in a growth medium in the laboratory over a period of time and subjected to chemotherapy drugs or drug combinations (ChemoFX, 2009). 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.

Huh et al. (2011) reported response rates of 755 endometrial specimens using the Chemo FX assay. An average of four chemotherapy regimens was tested for each specimen. The in vitro response rates were compared with population response rates. Although response rates reflected by assay results were generally consistent with published population rates, uncontrolled study design and the lack of comparison of the ChemoFx prediction of response and actual patient outcomes are limitations of the study.

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 accuracy rate was 75%.

In an effort to determine the effectiveness of ChemoFX in predicting response to chemotherapy measured in progression-free interval, Gallion et al. (2006) reported results of a retrospective study of 317 patients with ovarian tumors. Specimens from surgically excised ovarian carcinomas were submitted for testing via the ChemoFx assay. A statistically significant correlation between assay prediction of response and PFI was observed in 256 cases with an exact or partial match between drug(s) assayed and received. This study was limited by retrospective design and the lack of a control group for comparison.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. Several RCTs are ongoing. At this time the clinical utility of this assay has not been established.

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. The assay is proposed for use for an individual patient prior to the initiation of a chemotherapy drug or drugs in treatment.

Strickland et al. reported outcomes of a prospective observational correlational study reporting the results of the MiCK® assay regarding the rate of apoptosis in cells from blood or bone marrow aspirate of 109 adults with previously untreated acute myeloid leukemia. The study spanned 14 years beginning in 1996 through 2010 and involved two patient cohorts. The rate of apoptosis for each drug as noted by the MiCK® assay was significantly correlated with the complete response and overall survival rates for each individual for chemotherapy drugs noted to have greater apoptosis activity. Use of the MiCK® assay did not change clinical management as the chemotherapy regimen was selected by the treating physician based on best medical practice/standard of care and the treating physician was blinded to MiCK® assay results.

Salom et al. (2012) reported results of a prospective, nonrandomized observational trial to determine if a chemotherapy-induced apoptosis assay (MiCK) could predict the best therapy for 104 evaluable patients with ovarian cancer. Patients with epithelial ovarian cancer of any stage, primary or recurrent, were eligible. Overall survival in primary therapy, chemotherapy naïve patients with Stage III or IV disease was longer if patients received a chemotherapy which was best in the MiCK assay, compared to shorter survival in patients who received a chemotherapy that was not the best (p < 0.01, hazard ratio HR 0.23). Multivariate model risk ratio showed use of the best chemotherapy in the MiCK assay was the strongest predictor of overall survival (p < 0.01) in stage III or IV patients. Relapse-free interval in primary therapy patients was longer if patients received the best chemotherapy from the MiCK assay (p = 0.03, HR 0.52). Response rates were higher if physicians used an active chemotherapy based on the MiCK assay (p = 0.03). Study limitations included uncontrolled trial design and short-term follow-up.

Bosserman et al. (2012) reported results of an observational prospective nonblinded clinical trial in 44 patients with breast cancer (n16), nonsmall cell lung cancer (n=6), non-Hodgkin lymphoma (n=4) and other diagnoses to determine the effect of a drug-induced apoptosis assay results on treatment planned by oncologists. Patients with cancer of any stage, primary or recurrent, were eligible. Four patients received adjuvant chemotherapy after MiCK, and 40 received palliative chemotherapy. There were no rules or directions regarding how to use the MiCK assay results. The study evaluated whether the oncologist used the results of the assay, other data were also used (e.g., estrogen receptor analysis or human epidermal growth receptor 2 [HER2] test results, or addition of other drugs), or whether the assay results were not used. Oncologists used the MiCK assay to determine chemotherapy users in 28 (64%) and did not (nonusers) in 16 patients (36%). In users receiving palliative chemotherapy, complete plus partial response rate was 44%, compared with 6.7% in nonusers (P < .02). The median overall survival was 10.1 months in users versus 4.1 months in nonusers (P = .02). Relapse-free interval was 8.6 months in users versus 4.0 months in nonusers (P <.01). Limitations include uncontrolled study design, short follow-up, and small patient populations.

Ballard et al. (2010) reported results of a study of 19 individuals with endometrial cancer. Tumors were analyzed with the 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.

Evidence is insufficient evidence to demonstrate the impact of microculture kinetic assay of apoptosis (MiCK) on the clinical management of the patient. Whether outcomes are improved compared with management based on best current therapy/standard of care is not known; the use of in vitro assays to detect chemosensitivity has not yet been 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 a clinically useful prediction of response to therapy and patient survival as demonstrated by outcomes in high-quality, controlled clinical trials. Data are not robust; peer-reviewed published data are primarily observational, correlational studies. 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. □

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. 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.

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.

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.

Hur et al. (2012) reported outcomes of a randomized clinical trial designed to determine effectiveness of adenosine triphosphate-based chemotherapy response assay (ATP-CRA)-guided neoadjuvant chemotherapy for increasing resectability in 63 patients with unresectable colorectal liver metastasis. Patients were randomized into two groups: Group A (n=32) was treated by conventional chemotherapy regimen and Group B (n=31) was treated by chemotherapy regimen according to the ATP-CRA. Treatment response and resectability were compared between Group A and B. Median follow-up was 12 months. Group B showed better treatment response than group A (48.4% versus 21.9%, p=0.027). The resectability of the hepatic lesion was significantly higher in Group B than in Group A (35.5% versus 12.5%, P=0.032). According to multivariate logistic regression analysis, ATP-CRA was significantly associated with good treatment response (p=0.004) and liver resection (p=0.009). Data suggest improved resectability with use of the ATP response assay in this patient group; however, additional well designed RCTs are needed to determine applicability into routine clinical practice.

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.

Ugurel et al. (2006) reported outcomes of a multicenter phase II randomized controlled trial investigating the efficacy of assay-directed, first-line chemotherapy for patients with melanoma who had no distinct alterative to empirical therapy. ATP assay was used for patients with metastasis. The study groups were divided into 22 chemotherapy-sensitive patients and 31 chemotherapy-resistant patients. Objective response and OS were 36.4% and 14.6 months, respectively, in the chemotherapy-sensitive group, and 16.1% and 7.4 months, respectively, in the chemotherapy resistant group. There was no comparison between the two therapeutic interventions.

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.

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.

In a recent correlation study, Lee et al. (2012) reported sensitivity of fresh tumor samples from 79 patients with epithelial ovarian cancer to 11 chemotherapy agents. Retrospective analysis was performed. Among the 37 patients with International Federation of Gynecology and Obstetrics (FIGO) stage III/IV serous adenocarcinoma who were receiving carboplatin combined with paclitaxel, those with carboplatin-sensitive samples on HDRA had a significantly longer median disease-free interval than patients with carboplatin-resistant samples (p < 0.05), but median overall survival did not differ significantly (p = 0.621). 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%.

Further evaluation is warranted to confirm the relationship between results of the histoculture drug response assay (HDRA) and clinical responses. 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.

Summary for Chemosensitivty 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. At this time in vitro chemosensitivity and chemoresistance assays 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, updated 2011): On behalf of the ASCO Working Group, Burstein et al. (2011) published updated recommendations on the use of chemotherapy sensitivity and chemoresistance assays to select chemotherapeutic agents for individual patients. According to the Practice Guideline "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 based on 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™): NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer (2014) note "Chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN centers to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; however, the current level of evidence (category 3) is not sufficient to supplant standard of care chemotherapy. Thus the NCCN panel felt that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3), owing to the lack of demonstrable efficacy for such an approach."

Use Outside of the US
No relevant information.

Summary
Although numerous uncontrolled clinical trials have been conducted, standards have not been established for the use of tumor in vitro chemosensitivity or chemoresistance assays in clinical practice. To date the majority of studies have been small in participant numbers, correlational in design, and do not evaluate outcomes of individuals receiving assay-directed therapy compared to those who receive empiric-driven therapy. 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 yet been established.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered when used to report tumor 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

 *Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.

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