



Louisiana

In Vitro Chemoresistance and Chemosensitivity Assays

Policy # 00288

Original Effective Date: 03/16/2011

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers in vitro chemosensitivity assays, including, but not limited to, the Histoculture Drug Response Assay, a fluorescent cytoprint assay, the ChemoFx^{®†} assay, or the CorrectChemo^{®†} assay to be **investigational**.*

Based on review of available data, the Company considers in vitro chemoresistance assays, including, but not limited to, Extreme Drug Resistance assays to be **investigational**.*

Background/Overview

A variety of chemosensitivity and chemoresistance assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and nonviable cells to quantify cell kill following exposure to a drug of interest. With few exceptions, drug doses used in the assays are highly variable depending on tumor type and drug class, but all assays require drug exposures ranging from several-fold below physiologic relevance to several-fold above physiologic relevance. Although a variety of assays examine chemosensitivity or chemoresistance, only a few are commercially available. Available assays are outlined as follows.

Methods Using Differential Staining/Dye Exclusion

Differential Staining Cytotoxicity Assay

The Differential Staining Cytotoxicity assay relies on dye exclusion of live cells after mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation. Cells are then established in culture and treated with the drugs of interest at 3 dose levels: the middle (relevant) dose, which could be achieved in therapy; a 10-fold lower dose than the physiologically relevant dose; and a 10-fold higher dose. Exposure time ranges from 4 to 6 days; then cells are restained with fast green dye and counterstained with hematoxylin and eosin (H&E). The fast green dye is taken up by dead cells and H&E differentiates tumor cells from normal cells. The intact cell membrane of a live cell precludes staining with the green dye. Drug sensitivity is measured by the ratio of the number of live cells in the treated samples to the number of live cells in the untreated controls.

EVA/PCD Assay

The EVA/PCD assay (Rational Therapeutics, Long Beach, CA) relies on ex vivo analysis of programmed cell death, as measured by differential staining of cells after apoptotic and nonapoptotic cell death markers in tumor samples exposed to chemotherapeutic agents. Tumor specimens obtained through biopsy or

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surgical resection are disaggregated using DNase and collagenase IV to yield tumor clusters of the desired size (50-100 cell spheroids). Because these cells are not proliferated, these microaggregates are believed to more closely approximate the human tumor microenvironment. These cellular aggregates are treated with the dilutions of the chemotherapeutic drugs of interest and incubated for 3 days. After drug exposure is completed, a mixture of nigrosin B and fast green dye with glutaraldehyde-fixed avian erythrocytes is added to the cellular suspensions. The samples are then agitated and cytopsin-centrifuged and, after air drying, counterstained with H&E. The end point of interest for this assay is cell death, as assessed by observing the number of cells differentially stained due to changes in cellular membrane integrity.

Fluorometric Microculture Cytotoxicity Assay

The fluorometric microculture cytotoxicity assay is another cell viability assay that relies on the measurement of fluorescence generated from cellular hydrolysis of fluorescein diacetate to fluorescein in viable cells. Cells from tumor specimens are incubated with cytotoxic drugs; drug resistance is associated with higher levels of fluorescence.

Methods Using Radioactive Precursors by Macromolecules in Viable Cells

Tritiated Thymine

Tritiated thymine incorporation measures uptake of tritiated thymidine by DNA of viable cells. Using proteases and DNase to disaggregate the tissue, samples are seeded into single-cell suspension cultures on soft agar. They are then treated with the drug(s) of interest for 4 days. After 3 days, tritiated thymidine is added. After 24 hours of additional incubation, cells are lysed, and radioactivity is quantified and compared with a blank control consisting of cells that were treated with sodium azide. Only cells that are viable and proliferating will take up the radioactive thymidine. Therefore, there is an inverse relationship between uptake of radioactivity and sensitivity of the cells to the agent(s) of interest.

Extreme Drug Resistance Assay

The Oncotech Extreme Drug Resistance (EDR; Exiqon Diagnostics, Tustin, CA; no longer commercially available) is methodologically similar to the thymidine incorporation assay, using metabolic incorporation of tritiated thymidine to measure cell viability; however, single cell suspensions are not required, so the assay is simpler to perform. Tritiated thymidine is added to the cultures of tumor cells, and uptake is quantified after various incubation times. Only live (resistant) cells will incorporate the compound. Therefore, the level of tritiated thymidine incorporation is directly related to chemoresistance. The interpretation of the results is unique in that resistance to the drugs is evaluated, as opposed to evaluation of responsiveness. Tumors are considered to be highly resistant when thymidine incorporation is at least 1 standard deviation above reference samples.

Methods Quantifying Cell Viability Using Colorimetric Assay

Histoculture Drug Resistance Assay

The Histoculture Drug Resistance Assay (HDRA; AntiCancer Inc., San Diego, CA) evaluates cell growth after chemotherapy treatment based on a colorimetric assay that relies on mitochondrial dehydrogenases in living cells. Drug sensitivity is evaluated by quantification of cell growth in the 3-dimensional collagen matrix.

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There is an inverse relation between the drug sensitivity of the tumor and cell growth. Concentrations of drug and incubation times are not standardized and vary depending on drug combination and tumor type.

Methods Using Chemoluminescent Precursors by Macromolecules in Viable Cells Adenosine Triphosphate Bioluminescence Assay

The adenosine triphosphate (ATP) bioluminescence assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured and then exposed to drugs. Following incubation with drug, the cells are lysed and the cytoplasmic components are solubilized under conditions that will not allow enzymatic metabolism of ATP. Luciferin and firefly luciferase are added to the cell lysis product. This catalyzes the conversion of ATP to adenosine di- and monophosphate, and light is emitted proportionally to metabolic activity. This is quantified with a luminometer. From the measurement of light, the number of cells can be calculated. A decrease in ATP indicates drug sensitivity, whereas no loss of ATP suggests the tumor is resistant to the agent of interest.

ChemoFX Assay

The ChemoFX (Helomics Corp., previously called Precision Therapeutics, Pittsburgh, PA) assay also relies on quantifying ATP based on chemoluminescence. Cells must be grown in a monolayer rather than in a 3-dimensional matrix.

Methods Using Differential Optical Density

CorrectChemo Assay

Similar to the EVA/PCD assay, the CorrectChemo (previously called the Microculture Kinetic [MiCK]) assay; DiaTech Oncology, Franklin, TN) assay relies on measures of programmed cell death. In the assay, tumor cells are exposed to multiple concentrations of drugs and cultured. The optical density of the cells is measured over time, to create a density-by-time curve. A sudden increase in optical density is associated with cell apoptosis; the extent of drug-induced apoptosis is a measure of the cell's sensitivity to that agent. As of March 2016, DiaTech no longer offers the CorrectChemo assay commercially.

The rationale for chemosensitivity assays is strongest when there are a variety of therapeutic options and there are no clear selection criteria for any particular regimen in an individual patient.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Chemoresistance and chemosensitivity assays discussed in this review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

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Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

A variety of studies have reported a correlation between in vitro prediction or response and clinical response. While these studies may have internal validity, they cannot answer whether patients given assay-guided therapy or empiric therapy have different outcomes. To determine whether assay-guided treatment results in overall different outcomes than empirical treatment, it is important to take into account response rates, survival, adverse effects, and quality of life (QOL). These effects may be assessed indirectly (eg, using decision analysis) or directly with comparative trials. Both the 2002 TEC Assessment and the 2004 systematic review recommended validating chemotherapy resistance and sensitivity assays with direct evidence gathered from prospective trials comparing patients treated empirically with patients treated with assay-directed therapy. In this way, not only can response rates and survival be taken into account, but also adverse events (eg, from the toxic effects of an ineffective drug or delay or loss of benefits of an effective drug) and QOL.

The evaluation of a prognostic genetic test or related testing (ie, promoter methylation) focuses on 3 main principles: (1) analytic validity (technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (prognostic performance of a test [sensitivity, specificity, positive and negative predictive values] in predicting course of clinical disease); and (3) clinical utility (ie, a demonstration that the prognostic information can be used to improve patient health outcomes).

CHEMORESISTANCE AND CHEMOSENSITIVITY ASSAYS

Clinical Context and Test Purpose

The purpose of chemoresistance and chemosensitivity assays in patients who have cancer is to inform the decision on selecting treatment regimens.

The question addressed in this evidence review is: Does the use of chemoresistance and chemosensitivity assays improve the net health outcome in individuals with cancer?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with cancer.

Interventions

Chemoresistance and chemosensitivity assays differ with respect to processing of biologic samples and detection methods, but all involve: (1) isolation of cancer cells and establishment in an in vivo medium; (2) incubation of cells with various drugs; (3) assessment of cell survival; and (4) interpretation of results.

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Comparators

The relevant comparator of interest is physician-choice of chemotherapy, without information from chemoresistance assays or chemosensitivity assays.

Outcomes

The general outcome of interest is to determine cancer cell viability following exposure to a cancer drug. An accurate determination of cancer cell viability to a particular drug can then inform the decision on which drug treatment will be most effective. The specific outcome of interest is survival (progression-free and/or overall). Improved QOL is also an important goal of an effective treatment regimen.

False-positive and false-negative test results can lead to the patient receiving a treatment regimen that is not potentially the most effective.

Timing

Chemoresistance and chemosensitivity assays can be performed on fresh tumor tissue samples of newly diagnosed or recurrent cancer patients.

Setting

Cancer cells are obtained through clinically indicated surgery or biopsy. The samples are shipped to a laboratory conducting the chemoresistance or chemosensitivity assays.

Chemoresistance Assays

Chemoresistance assays are used to deselect potential chemotherapeutic regimens. The negative predictive value (NPV) is a key statistical measure. Unless the NPV is high, there is a chance that clinical decision making based on a chemoresistance assay could inappropriately exclude an effective therapy. The NPV will vary according to the prior probability of chemoresistance as well as the assay's sensitivity and specificity. The 2002 TEC Assessment concluded that chemoresistance assays have the highest clinical relevance in tumors with a low probability of response. The Extreme Drug Resistance (EDR) assay was specifically designed to produce a very high NPV (>99%), such that the possibility of inappropriately excluding effective chemotherapy is remote in all clinical situations.

To determine whether chemoresistance assays have value in clinical decision making, studies comparing outcomes for patients managed using chemoresistance assays with those managed using routine care would be ideal. Potential relevant clinical outcomes include improved survival and avoidance of toxicity (as an intermediate outcome).

The bulk of the literature on EDR assays have focused on correlational studies assessing results from predictive in vitro assays and observed outcomes of chemotherapy. However, in these studies, patients do not receive assay-guided chemotherapy regimens. As discussed in the 2004 systematic review, correlational studies are inadequate to demonstrate the clinical utility of chemoresistance assays for several reasons. First, such studies often aggregate patients with different tumor types, disease characteristics,

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chemotherapy options, and probabilities of response. This process is problematic because the accuracy of each assay used to predict in vivo response probably varies across different malignancies and patient characteristics. Second, the method by which assay results are translated into treatment decisions is not standardized. Third, it is important to consider not only response but also survival, QOL, and adverse effects. The overall value of assay-guided therapy depends on the net balance of all health outcomes observed after treatment for all patients subjected to testing, regardless of assay results or the accuracy of its predicted response. Examples of some of the earlier published correlation studies of the EDR assay include those by Eltabbakh et al (1998, 2000), Mehta et al (2001), Holloway et al (2002), and Ellis et al (2002).

The 2002 TEC Assessment identified a nonrandomized retrospective comparative study by Loizzi et al (2003) using the EDR assay. (While this study of patients with recurrent ovarian cancer found a significantly higher overall response rate, better progression-free survival (PFS), and higher overall survival (OS) among platinum-sensitive patients receiving assay-guided therapy, it was not designed to address potential biases and confounding adequately. Since the Loizzi study, no additional comparative studies of assay-guided therapy vs physician-directed therapy have appeared for chemoresistance assays.

Clinical Validity

Clinical validity is the ability of a test to measure accurately and reliably the marker of interest. Measures of analytic validity include sensitivity (detection rate), specificity (1– false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

Prospective Studies

A study by Tiersten et al (2009) used the Oncotech EDR assay to examine whether chemotherapy resistance was an independent predictor of PFS in patients with stage III or IV ovarian cancer. Fifty-eight eligible women were prospectively enrolled in this study; however, results from the EDR assay were not used to direct therapy. All women were treated with neoadjuvant chemotherapy and surgical cytoreduction followed by intraperitoneal chemotherapy. Evaluable EDR assay results were available for 22 patients. No difference in PFS was reported among patients who were defined as “resistant” or “nonresistant” to platinum or paclitaxel based on the EDR assay. Follow-up was not sufficient to measure OS. These data do not support the use of the EDR assay in predicting outcome and guiding patient management.

A 2006 review by Nagourney included 21 noncomparative studies using ex vivo programmed cell death assays. Selected studies correlated drug susceptibility findings for the ex vivo assay for those with an objective clinical response (complete or partial) and nonresponders (total 659 N=patients). Nagourney obtained aggregate positive values by the site of primary cancer: breast (82.9%), colon (80%), non-small-cell lung cancer (66.7%), gynecologic (77%), and small-cell lung cancer (50%). A 2012 study by this same investigator prospectively assessed 98 patients with non-small-cell lung cancer treated between 2003 and 2010. Only 41 were eligible for inclusion and tested with the EVA/PCD assay to determine which chemotherapeutic drugs to use. Another 10 patients were excluded (5 due to insufficient cellular yield, 3 for resistance to all drugs tested, 2 due to physician’s choice), yielding only 31 patients who received the

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assay-recommended treatment. The authors compared results for these 31 patients treated using assay-directed chemotherapy with historical controls (not described) on the outcome of observed objective response rate (complete response and partial response). The objective response rate was 64.5% (95% confidence interval [CI], 46.9% to 78.9%) for the assay-directed chemotherapy group, which was significantly greater than the historic standard rate of 30% objective response ($p < 0.001$).

Retrospective Studies

In 2010, Matsuo et al published a study examining the relevance of extreme drug resistance in epithelial ovarian carcinomas. Two hundred fifty-three records from the Oncotech database were identified for women with advanced stage ovarian cancer and from whom samples were collected at the time of the primary surgery. Tissue samples were cultured and tested for response to primary drugs (4 platinum- or taxane-based) and secondary drugs (eg, gemcitabine, topotecan, doxorubicin, etoposide, 5-fluorouracil). Paclitaxel showed the highest resistance rate. Other agents had a resistance rate of less than 20%. Only 1 (0.4%) tumor showed complete resistance to all drugs tested, and 25% of tumors showed no resistance to any of the drugs. There was no statistical correlation between assay results and response to initial chemotherapy. Investigators acknowledged that the study, due to its retrospective and noncomparative design, was not sufficiently strong to validate the use of this assay in managing therapy. Potential confounding factors, described by investigators, may have included tumor heterogeneity and variations in resistance between primary tumor and metastases.

Another study (2009) by the same group evaluated the potential of the EDR assay to guide the selection of platinum- and taxane-based therapies for the management of patients with advanced epithelial ovarian, fallopian, and peritoneal cancers. From the Oncotech database, 173 cases were identified. For all cases, tissue was collected at the time of cytoreductive therapy. The EDR assay was performed on all samples, and tumors were classified as having low drug resistance, intermediate drug resistance, or extreme drug resistance. The 58 (33.5%) patients whose tumors had low drug resistance to both platinum and taxane showed statistically improved 5-year PFS and OS compared with the 115 (66.5%) patients who demonstrated intermediate or extreme drug resistance to platinum and/or taxane (5-year OS rates, 41.1% vs 30.9%, respectively; $p = 0.014$). The 5-year OS rate of the 28 (16.2%) cases who had optimal cytoreduction with low drug resistance to both platinum and taxane (54.1%) was significantly better than that for the 62 (35.8%) cases who were suboptimally cyto-reduced with intermediate or extreme drug resistance to platinum and/or taxane (20.4%; $p < 0.001$). Although the EDR assay was predictive for survival, assay results did not indicate a response to therapy with taxane or cisplatin. The investigators concluded that the EDR assay might be an independent predictor of PFS and OS; however, a prospective, randomized trial would be required to further assess its clinical utility in predicting response to taxane or platinum therapies.

In a smaller study (N=51) by Matsuo et al (2010) testing predictive value of the EDR assay for uterine carcinosarcoma response to taxane and platinum was also conducted, 31 (60.8%) patients received postoperative chemotherapy with at least a single agent and 17 (33.3%) received combination chemotherapy with platinum and taxane modalities. Overall response rate for the 17 combination

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chemotherapy cases was 70.6%. The presence of extreme drug resistance to either platinum or taxane showed a significantly lower 1-year PFS rate (28.6% vs 100%, respectively; $p=0.01$) and lower 5-year OS rate (26.9% vs 57.1%, respectively; $p=0.033$). These data would indicate that use of an in vitro drug resistance assay may be predictive of response to chemotherapy response and survival outcome in advanced ovarian and uterine carcinosarcoma. However, larger, prospective, randomized controlled trials would be required to validate the use of this assay for directing chemotherapy regimens.

Matsuo et al (2010) also compared the rates of extreme drug resistance after cytoreductive therapy and neoadjuvant chemotherapy with the rates of extreme drug resistance after postoperative chemotherapy. The goal of this study was not to test whether the EDR assay could direct therapeutic regimens. The findings suggested that platinum resistance was most common after neoadjuvant chemotherapy, while paclitaxel resistance was more prevalent after postoperative chemotherapy.

Karam et al (2009) retrospectively reviewed 377 patients with epithelial ovarian cancer to examine the effect of EDR assay-guided therapy on outcomes in the primary and recurrent setting. The primary end points were time to progression, OS, and survival after recurrence. The patient population was heterogeneous, with a median age of 59 years (range, 24-89 years), and 30% of patients had completely resected tumors, and were enrolled at varying tumor stages (Federation of Gynecologists and Obstetricians stages I, II, III, and IV in 7%, 4%, 78%, and 11%, respectively). Sixty-four percent of patients underwent a secondary cytoreductive surgery. Patients had an EDR assay sent either at the time of their primary cytoreductive surgery ($n=217$) or at the time of disease recurrence ($n=160$). Predictors of survival included increasing age and greater volume of residual disease after cytoreductive surgery. EDR assay results analyzed for single agents or combinations of chemotherapies failed to predict patient outcomes independently whether the assay was performed at the time of the primary surgery or at recurrence.

Hetland et al (2012) studied primary platinum resistance in epithelial ovarian cancer patients with Federation of Gynecologists and Obstetricians stage III or IV disease. Eighty-five biopsies from 58 patients were included. Resistance was assessed with a modified drug response assay including ATP-based tumor chemosensitivity and EDR assay. Samples were tested for response to platinum, paclitaxel, and a combination of the drugs. Results from the assay were combined, and tumors were classified using a resistance index, which summarized the percentage of tumor growth inhibition for each drug concentration tested. All patients received a primary chemotherapy treatment of carboplatin, paclitaxel, or a combination of the 2 drugs. Platinum resistance, as defined by the risk index, was associated with significantly poorer PFS with a median value of 3.9 months (95% CI, 3.2 to 4.7 months) than platinum sensitivity with a median PFS of 8.1 months (95% CI, 3.7 to 12.4 months). Patients who had a partial response, stable disease, or progressive disease were more resistant to platinum-based chemotherapy on the risk index score than those with a complete response ($p=0.02$). In a subgroup analysis of metastatic tumors, platinum resistance was not associated with PFS or clinical response. Response to paclitaxel or carboplatin plus paclitaxel was not associated with PFS or clinical response. In vitro response was not associated with OS in any group.

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Clinical Utility

No studies comparing outcomes using assay-directed therapy with physician-chosen therapy were identified.

Section Summary: Chemoresistance Assays

Some retrospective and prospective studies have suggested that chemoresistance assays, particularly the EDR assay, may be associated with chemotherapy response. However, prospective studies do not consistently demonstrate that chemoresistance assay results are associated with survival. Furthermore, no comparative studies were identified that compared outcomes among patients managed with assay-directed therapy and those managed with physician-directed therapy.

Large, randomized, prospective clinical studies comparing outcomes, including OS and disease-specific survival, QOL, and adverse events, between assay-directed therapy and physician-directed therapy, are needed.

Chemosensitivity Assays

Chemosensitivity assays are designed to select the most appropriate chemotherapy regimens for a given tumor type, and would therefore ideally be associated with high positive predictive values for clinical response. The critical type of evidence needed to establish the effectiveness of chemosensitivity assays would come from comparative studies of assay-guided therapy vs physician-directed therapy. Relevant outcomes would include OS and disease-specific survival, as well as QOL and adverse events.

The 2002 TEC Assessment and 2004 systematic review identified 9 comparative studies, two of which were randomized. Selected studies reported that significant advantages for assay-guided therapy regarding tumor response did not translate into survival differences. Response rate differences seen in other nonrandomized comparative studies may be attributable to bias or confounding, and survival outcomes were rarely reported.

Clinical Validity

Prospective Studies

Kim et al (2010) reported on the results of a prospective, multicenter clinical trial designed to define the accuracy of the ATP-based chemotherapy response assay in gastric cancer patients receiving paclitaxel and cisplatin chemotherapy, by comparing clinical response and the ATP assay results. The primary end point of the study was to assess the accuracy of the ATP assay results, and the secondary end point was to find the best method of defining in vitro chemosensitivity. Forty-eight patients with chemotherapy-naïve locally advanced or metastatic gastric cancer were treated with combination chemotherapy after a tissue specimen was obtained for the ATP assay. Tumor response was assessed by World Health Organization criteria using a computed tomography scan after every 2 cycles of chemotherapy. Laboratory technicians and physicians were blinded to the assay or clinical results. Thirty-six patients were evaluable for both in vitro and in vivo responses. Using a chemosensitivity index method, the specificity of the ATP assay was 95.7% (95% CI, 77.2% to 99.9%), sensitivity was 46.2% (95% CI, 19.2% to 74.9%), positive predictive

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value was 85.7% (95% CI, 42.1% to 99.6%), and NPV was 75.9% (95% CI, 55.1% to 89.3%). Median PFS was 4.2 months (95% CI, 3.4 to 5.0 months) and median OS was 11.8 months (95% CI, 9.7 to 13.8 months). The in vitro chemosensitive group showed a higher response rate (85.7%) than the chemoresistant group (24.1%; $p=0.005$). The authors concluded that the ATP assay could predict clinical response to paclitaxel and cisplatin chemotherapy with high accuracy in advanced gastric cancer and that the study supported the use of the ATP assay in further validation studies.

Rutherford et al (2013) reported on results from a prospective, noninterventional, multicenter cohort study designed to assess whether the ChemoFX assay was predictive of outcomes among women (N=335) with histologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Patients were treated with 1 of 15 study protocols; treating physicians were blinded to the ChemoFX assay result. Two hundred sixty-two (78.2% of total) patients had both available clinical follow-up data and a ChemoFX result. Cancer cells were classified based on the ChemoFX result as sensitive, intermediate, or resistant to each of several chemotherapeutic agents. Patients treated with an assay-sensitive regimen had a median PFS of 8.8 months compared with 5.9 months for those with assay-intermediate or -resistant regimens (hazard ratio [HR], 0.67; $p=0.009$). Mean OS was 37.5 months for patients treated with an assay-sensitive regimen and 23.9 months for those with assay-intermediate or -resistant regimens (HR=0.67, $p=0.010$).

In a follow-up analysis, Tian et al (2014) evaluated whether the ChemoFX assay could predict PFS by comparing the association when the assayed therapy matched the administered therapy (match) with the association when the assayed therapy was randomly selected (mismatch). The authors generated a simulation in which the average prognostic value of assay results for multiple different therapies was generated using the assay results for mismatch, in which the assay result for a treatment was randomly selected from the (up to) 15 designated therapies with equal probability for each patient. Based on 3000 repeated simulated resamplings, the mean HR for cases of mismatch was 0.81 (reported as 95% range, 0.66-0.99), which the authors suggested indicated that patients with a mismatch had less benefit when treated with an assay-sensitive therapy. Strengths of this study included its prospective design with physicians blinded to the assay results, which reduced the risk of bias in patient selection and measurement of outcomes. However, because the selection of chemotherapeutic agent was, by design, not influenced by the ChemoFX assay, the impact on health outcomes could not be determined.

Krivak et al (2014) reported on results from a subsequent prospective, observational, multicenter study to determine whether sensitivity to carboplatin and/or paclitaxel is associated with disease progression among patients with primary epithelial ovarian cancer following initial treatment with a platinum plus taxane regimen. A total of 462 patients were enrolled, with 276 evaluable for analysis. Assay results for carboplatin and paclitaxel were available for 231 and 226 patients, respectively, with 44 (19.1%) patients identified as carboplatin-resistant and 49 (21.7%) identified as paclitaxel-resistant. Carboplatin-resistant patients were at a higher risk of disease progression than nonresistant patients (HR=1.87; 95% CI, 1.29 to 2.70; $p<0.001$).

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In a similar study design, Salom et al (2012) conducted a prospective, noninterventional, multicenter cohort study to assess whether the Microculture Kinetic (MiCK) assay (now called CorrectChemo) was predictive of outcomes among women with epithelial ovarian cancer. Data from 150 women with any stage of cancer with specimens suitable for MiCK assay were included. Chemosensitivity was expressed as kinetic units following each dose of the drug in the MiCK assay and reported as mean, minimum, and maximum. For each patient, the “best” chemotherapy was defined as any single drug or combination of drugs in the patient’s MiCK assay that had the highest kinetic units. Patients’ regimens were at the discretion of treating physicians, who were blinded to the MiCK assay results. OS for stage III or IV disease was longer if patients received a chemotherapy that was considered “best” by the MiCK assay, compared with shorter OS for patients who received a chemotherapy that was not the best (HR=0.23, $p<0.01$).

Jung et al (2013) conducted a single-center prospective study to determine whether sensitivity to paclitaxel and carboplatin, determined by using the Histoculture Drug Resistance Assay, was predictive of outcomes among 104 women with advanced epithelial ovarian cancer. All patients had undergone initial surgery and were treated with paclitaxel and carboplatin therapy. Tumor cell sensitivity to the chemotherapy agents was classified as sensitive, intermediate, or resistant to paclitaxel, carboplatin, or both, based on the Histoculture Drug Resistance Assay. Patients whose tumors were sensitive to both drugs had a lower recurrence rate than those with resistance to both drugs (29.2% vs 69.8%, $p=0.02$) and had a longer PFS (35 months vs 16 months; $p=0.025$).

In 2015, Zhang and Li evaluated ovarian epithelial cancer cells using an in vitro ATP tumor chemosensitivity assay. Specimens from 80 women with ovarian epithelial cancer who had undergone cytoreductive surgery were tested for sensitivity to 8 different treatments (paclitaxel, carboplatin, topotecan, gemcitabine, docetaxel, etoposide, bleomycin, 4-hydroperoxycyclophosphamide). Overall sensitivity, specificity, positive predictive value, and negative predictive value were 88.6%, 77.8%, 83.0%, and 84.8%, respectively. Specimens from the lower stage (I-II) ovarian epithelial cancer had lower chemosensitivity than advanced stage (III). High to mildly differentiated specimens had lower chemosensitivity than low differentiated specimens.

While these studies have established that the results of chemosensitivity assays correlate with outcome, they did not evaluate how the test might alter clinical decision making and whether changes in management based on the test would improve outcomes.

Retrospective Studies

A number of retrospective studies have evaluated the association between various chemosensitivity assays and clinical outcomes in several tumor types, most commonly epithelial ovarian cancer. Some representative studies are discussed next.

In 2016, Tanigawa et al published a retrospective study evaluating the association between in vitro chemosensitivity results and relapse-free survival in 206 gastric cancer patients. The collagen gel droplet embedded culture drug sensitivity test is commercially available as a kit in Japan. All patients underwent

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surgery and were then treated with S-1 (tegafur/gimeracil/oteracil) chemotherapy. In vitro sensitivity of resected tumor specimens to fluorouracil was used as a surrogate of in vitro sensitivity to S-1 (this approach had been previously validated by the research group). Tumors were categorized as in vitro sensitive (responders) or in vitro insensitive (nonresponders). The median length of follow-up from the time of surgery was 3.2 years. Three-year relapse-free survival was significantly higher in the in vitro sensitive (responder) group (82.9%; 95% CI, 74.4% to 91.3%) than in the in vitro insensitive (nonresponder) group (63.4%; 95% CI, 54.7% to 72.1%; $p=0.001$).

Gallion et al (2006) retrospectively evaluated the association between ChemoFX test results and the treatment response of 256 patients with ovarian or peritoneal cancer treated with at least 1 cycle of postsurgical chemotherapy. A subset of 135 patients had an exact match between drugs assayed and received; the rest had only a partial match. Predictive values were not reported or calculable. For the subset of 135, in a multivariable analysis, ChemoFX was an independent significant predictor ($p=0.006$) of PFS along with 2 other clinical variables. The HR for resistant vs sensitive was 2.9 (95% CI, 1.4 to 6.30) and was 1.7 (95% CI, 1.2 to 2.5) for resistant vs intermediate. The median PFS was 9 months for the resistant group, 14 months for the intermediate group, and had not been achieved at reporting for the sensitive group.

Herzog et al (2010) included 147 patients from the Gallion study and reported on 192 women with advanced stage primary ovarian cancer, 175 of whom had tumors tested for in vitro chemosensitivity to platinum therapy using ChemoFX. Tumors were classified as responsive, intermediately responsive, or nonresponsive to chemotherapy. Seventy-eight percent were categorized as responsive or intermediately responsive, and 22% were nonresponsive. Median OS was 72.5 months for patients with tumors categorized as responsive, 48.6 months for intermediately responsive, and 28.2 months for nonresponsive ($p=0.03$; HR=0.70; 95% CI, 0.50 to 0.97). The authors concluded that the results of chemosensitivity testing with a drug response marker for therapy were predictive of OS in patients with primary ovarian cancer.

In a smaller study, Grigsby et al (2013) retrospectively analyzed the association between pretreatment chemosensitivity to cisplatin and clinical outcomes in 33 women with cervical cancer. Tumor cell sensitivity to cisplatin was categorized as responsive, intermediately responsive, or nonresponsive with the ChemoFX assay. Patients with responsive or intermediately responsive tumors had a 2-year recurrence-free survival of 87% compared with 58% for those with nonresponsive tumors ($p=0.036$).

Lee et al (2012) conducted a retrospective study of Histoculture Drug Resistance Assay in 79 patients with ovarian cancer. Tissue samples were assessed for 11 chemotherapeutic agents and found the highest inhibition rates in carboplatin (49.2%), topotecan (44.7%), and belotecan (39.7%). These inhibition rates were higher than with cisplatin (34.7%), the traditional drug used to treat epithelial ovarian cancer. Outcomes for a subset of 37 patients with Federation of Gynecologists and Obstetricians stage II, III, or IV stage III or IV epithelial ovarian serous adenocarcinoma who had been treated with at least 3 cycles of carboplatin chemotherapy were compared between carboplatin-sensitive and -resistant patients. Multiple comparison and regression analyses established a cutoff value of 40% inhibition rate in response to 50 $\mu\text{g/mL}$ carboplatin to determine sensitivity or resistance. This selected cutoff had a disease-free survival of

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23.2 months (95% CI, 6.3 to 55.3 months) and 13.8 months (95% CI, 4.9 to 35.6 months) in the carboplatin-sensitive and carboplatin-resistant groups, respectively ($p < 0.05$). Mean OS between groups did not differ significantly, with carboplatin-sensitive patients having of 60.4 months and carboplatin-resistant patients having 37.3 months ($p = 0.621$).

Strickland et al (2013) retrospectively evaluated the association between chemosensitivity and anthracyclines, measured by the drug-induced apoptosis MiCK assay, among 109 patients with adult-onset acute myelogenous leukemia. Patients were treated with a “7 plus 3” chemotherapy regimen. Chemosensitivity was expressed as maximal kinetic units following each dose of the drug in the MiCK assay. Receiver operator characteristic curve analysis and logistic regression were used to determine the optimal cutoff for chemosensitivity response to discriminate between chemoresponder and nonresponder. Patients determined to be chemoresponders to idarubicin were more likely to have a complete response to chemotherapy (72%) than those who were nonresponders ($p = 0.01$). Data for the patient cohort were collected over 14 years, from 1996 to 2010, which might limit the generalizability of the results to currently used chemotherapy regimens.

Other retrospective studies have evaluated chemosensitivity results as measured by other assay types. Von Heideman et al (2014) evaluated the semi-automated fluorometric microculture cytotoxicity assay in 112 patients (125 samples) with ovarian cancer and concluded that samples from patients with clinical response were more sensitive to most drugs than samples from nonresponding patients.

Clinical Utility

A small number of nonrandomized studies have evaluated differences in outcomes between patients treated with assay-directed therapy and patient given with physician-chosen therapy.

In 2015, Bosserman et al published a prospective nonblinded study to determine if physicians who use the results from MiCK assays on breast cancer specimens have better patient outcomes than physicians who do not. Tumor samples were extracted from 30 women with recurrent or metastatic breast cancer and submitted for the MiCK drug-induced apoptosis assay. Results were available to physicians within 72 hours after the biopsy. Physicians could use or not use the test results to determine therapy. Most physicians (22/30) used the assay results to select the chemotherapy regimens for their patients. Of those using the assay results, 15 physicians changed the original treatment plans for their patients. Among physicians who did not use the assay results, reasons given included: patient refused the most active drugs indicated by the assay (4 patients), the physician did not want to use most active drugs indicated by the assay (2 patients), and unstated (2 patients). Complete response, partial response, and disease control were more frequently experienced in patients whose physicians used the assay results compared with patients whose physicians did not use the assay results ($p = 0.04$). Time to recurrence was significantly longer in patients whose physicians used the assay (7.4 months) compared with patients whose physicians did not (2.2 months). OS did not differ significantly between patients whose physicians used the assay (16.8 months) and patients whose physicians did not (13.1 months).

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In 2006, Ugurel et al conducted a nonrandomized, prospective phase 2 trial of 53 evaluable patients with metastatic melanoma. Biopsy samples from each patient were sent to a laboratory for chemosensitivity testing using the ATP tumor chemosensitivity assay. Patients then received assay-directed therapy with the drug or drug combination that had the highest in vitro sensitivity. Median follow-up was 19 months. The study found a 36% complete and partial response rate in patients with chemosensitive tumors compared with 16% in those with chemoresistant tumors.

In a case-control retrospective trial, Moon et al (2009) retrospectively compared ATP assay-based guided chemotherapy with empirical chemotherapy in unresectable non-small-cell lung cancer. All patients who received ATP assay-guided platinum-based doublet chemotherapy as first-line therapy received platinum-based chemotherapy combined with a nonplatinum drug, regardless of their in vitro platinum sensitivity; 14 patients had platinum-sensitive disease, and 13 were platinum-resistant. Ninety-three matched controls (matched for performance status, stage, and chemotherapy regimen) were selected from a retrospective review of a database. In the empirical group, a nonplatinum drug was chosen, depending on physicians' discretion, along with a platinum agent determined by renal function and performance status. The primary end point was clinical response rate, assessed every 2 cycles of chemotherapy by the Response Evaluation Criteria in Solid Tumors criteria. The secondary end points were PFS and OS. Response and survival rates in both groups did not differ statistically. By ATP assay, the platinum-sensitive subgroup (71%) showed a higher response rate than the empirical group (38%; $p=0.02$), but PFS and OS differences between groups were not statistically significant.

In a nonrandomized prospective study (N=64), Iwahashi et al (2005) reported on outcomes of chemosensitivity-guided chemotherapy compared with standard chemotherapy and no chemotherapy in patients with advanced gastric cancer who had undergone a gastrectomy. Among patients with stage IV gastric cancer, the 5-year OS rate was 38% in the chemosensitivity-guided chemotherapy group and 0% in the standard chemotherapy and no chemotherapy groups. Among patients with para-aortic node involvement, survival was significantly greater in the chemosensitivity-guided group than in with the standard and no chemotherapy groups. However, survival was equivalent between the groups when there was no para-aortic node involvement.

Cree et al (2007) reported on a prospective RCT of chemosensitivity assay-directed chemotherapy vs physician's choice in patients with recurrent platinum-resistant ovarian cancer. The primary aim of this randomized controlled trial was to determine response and PFS rates following chemotherapy in patients treated according to an ATP-based tumor chemosensitivity assay and treated by physician-choice. A total of 180 patients were randomized to assay-directed therapy (n=94) or to physician-choice chemotherapy (n=86). Median follow-up at analysis was 18 months; the response was assessable in 147 (82%) patients: 31.5% achieved a partial or complete response in the physician-choice group compared with 40.5% in the assay-directed group (26% vs 31% by intention-to-treat analysis, respectively). Intention-to-treat analysis showed a median PFS of 93 days in the physician-choice group and 104 days in the assay-directed group (HR=0.8; $p=0.14$). No difference was seen in OS between groups, although 12 (41%) of 39 patients who crossed over from the physician-choice arm obtained a response. Increased use of combination therapy

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was seen in the physician-choice arm during the trial as a result of the observed effects of assay-directed therapy in patients. The authors concluded that this small randomized controlled trial suggested a trend toward improved response and PFS for assay-directed treatment and that chemosensitivity testing might provide useful information in some patients with ovarian cancer. They also noted that the ATP-based tumor chemosensitivity assay would remain an investigational method in this condition.

Section Summary: Chemosensitivity Assays

The most direct evidence related to the effectiveness of chemosensitivity assays in the management of patients with cancer comes from several studies that compare outcomes for patients managed using an ATP-based tumor chemosensitivity assay with those managed using standard care, including a randomized controlled trial. Although some improvements in tumor response were noted, no differences between OS or PFS were seen. A number of retrospective and prospective studies of several different chemosensitivity assays, including the ATP-based tumor chemosensitivity assay, the CorrectChemo assay, and the ChemoFX assay, have suggested that patients whose tumors have higher chemosensitivity have better outcomes. However, additional studies to determine whether the clinical use of in vitro chemosensitivity testing leads to better outcomes are needed.

SUMMARY OF EVIDENCE

For individuals who have cancer who are initiating chemotherapy who receive chemoresistance assays, the evidence includes correlational observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and quality of life. Some retrospective and prospective correlational studies have suggested that chemoresistance assays may be associated with chemotherapy response. However, prospective studies have not consistently demonstrated that chemoresistance assay results are associated with survival. Furthermore, no studies were identified that compared outcomes for patients managed using assay-directed therapy with those managed using physician-directed therapy. Large, randomized, prospective clinical studies comparing overall survival are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who are initiating chemotherapy who receive chemosensitivity assays, the evidence includes a randomized controlled trial, nonrandomized studies, and correlational observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and quality of life. The most direct evidence on the effectiveness of chemosensitivity assays in the management of patients with cancer comes from several studies comparing outcomes for patients managed using a chemosensitivity assay with those managed using standard care, including a randomized controlled trial. Although some improvements in tumor response were noted in the randomized controlled trial, there were no differences in survival outcomes. One small nonrandomized study reported improved overall survival in patients receiving chemosensitivity-guided therapy compared with patients receiving standard chemotherapy. A number of retrospective and prospective studies of several different chemosensitivity assays have suggested that patients whose tumors have higher chemosensitivity have better outcomes. Currently, additional studies to determine whether the clinical use of in vitro chemosensitivity testing leads

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to improvements in overall survival are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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| 03/03/2011 | Medical Policy Committee review |
| 03/16/2011 | Medical Policy Implementation Committee approval. New policy. |
| 03/01/2012 | Medical Policy Committee review |
| 03/21/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 03/07/2013 | Medical Policy Committee review |
| 03/20/2013 | Medical Policy Implementation Committee approval. No change to coverage. |
| 03/06/2014 | Medical Policy Committee review |
| 03/19/2014 | Medical Policy Implementation Committee approval. No change to coverage. |
| 05/07/2015 | Medical Policy Committee review |
| 05/20/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 05/05/2016 | Medical Policy Committee review |
| 05/18/2016 | Medical Policy Implementation Committee approval. "ChemoFx" and "CorrectChemo" added to the list of investigational chemosensitivity assays; policy statements otherwise unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 05/04/2017 | Medical Policy Committee review |
| 05/17/2017 | Medical Policy Implementation Committee approval. No change to coverage. |
| 05/03/2018 | Medical Policy Committee review |
| 05/16/2018 | Medical Policy Implementation Committee approval. No change to coverage. |
- Next Scheduled Review Date: 05/2019

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Louisiana

In Vitro Chemoresistance and Chemosensitivity Assays

Policy # 00288

Original Effective Date: 03/16/2011

Current Effective Date: 05/16/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81535, 81536, 87230, 88104
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be law fully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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