Replaced by MolDX
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BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

In Vitro Chemoresistance and Chemosensitivity Assays

Policy #: 097
Latest Review Date: May 2015
Category: Laboratory

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

In vitro chemoresistance and chemosensitivity assays have been developed to provide information about the characteristics of an individual patient's malignancy to predict potential responsiveness of their cancer to specific drugs. These assays are sometimes used by oncologists to select treatment regimens for an individual patient. Several assays have been developed that differ with respect to processing of biological samples and detection methods. However, all involve similar principles and share protocol components including: 1) isolation of cells and establishment in an in vitro medium (sometimes in soft agar); 2) incubation of the cells with various drugs; 3) assessment of cell survival; and 4) interpretation of the result.

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 exist to examine chemosensitivity or chemoresistance, only a few are commercially available. Available assays are outlined as follows:

Methods using differential staining/dye exclusion:

- The Differential Staining Cytotoxicity (DiSC) Assay. This 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 three dose levels; the middle dose is that which could be achieved in therapy; ten-fold lower than the physiologically relevant dose; and, ten-fold higher. Exposure time ranges from four to six 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 can differentiate 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 live cells in the treated samples to the number of live cells in the untreated controls.

- The EVA/PCD™ assay (available from Rational Therapeutics, Long Beach, CA). This assay relies on ex-vivo analysis of programmed cell death, as measured by differential staining of cells after apoptotic and non-apoptotic cell death markers in tumor samples exposed to chemotherapeutic agents. Tumor specimens obtained through biopsy or surgical resection are disaggregated using DNAse and collagenase IV to yield tumor clusters of the desired size (50 to 100 cell spheroids). Because these cells are not proliferated, these micro-aggregates are believed to more closely approximate the human tumor micro-environment. These cellular aggregates are treated with the dilutions of the chemotherapeutic drugs of interest and incubated for three days. After drug exposure is completed, a mixture of Nigrosin B & Fast Green dye with glutaraldehyde-fixed avian erythrocytes are added to the cellular suspensions. The samples are then agitated and cytospin-centrifuged and, after air drying, are counter-stained with H&E. The endpoint 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.

- The fluorometric microculture cytotoxicity assay (FMCA) 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 incorporation of radioactive precursors by macromolecules in viable cells:

- 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 four days. After three days, tritiated thymidine is added. After 24 hours of additional incubation, cells are lysed, and radioactivity is quantified and compared to 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 update of radioactivity and sensitivity of the cells to the agent(s) of interest.

- The Extreme Drug Resistance assay (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 one standard deviation (SD) above reference samples

Methods to quantify cell viability by colorimetric assay:

- The Histoculture Drug Resistance Assay (HDRA; AntiCancer Inc., San Diego, CA). This assay 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. There is an inverse relationship 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 incorporation of chemoluminescent precursors by macromolecules in viable cells:

- The Adenosine Triphosphate (ATP) Bioluminescence Assay. This assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, 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 that the tumor is resistant to the agent of interest.

- ChemoFX® (Helomics Corporation, previously called Precision Therapeutics, Pittsburgh, PA). This 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® (previously called the Microculture Kinetic [MiCK] Assay) (Diatech Oncology, Franklin, TN). Similar to the EVA/PCD assay, this 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.

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

Policy:

Effective for dates of service on or after January 1, 2016 refer to MolDX.

Effective for dates of service on or after July 1, 2005 through December 31, 2015:
Blue Advantage will treat **In Vitro Chemosensitivity and Chemoresistance Assays** including but not limited to histoculture drug response assays, a fluorescent cytoprint assay, the ChemoFx assay, the CorrectChemo assay, or extreme drug resistance assays (i.e., Thymidine Incorporation Assay, MTT Assay, ATP-Cell Viability Assay, DiSC Assay, EDR Assay, and HDRA) as a **non-covered** benefit and as **investigational. Refer to CMS NCD 190.7, Human Tumor Stem Cell Drug Sensitivity Assays.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The policy has been updated with periodic literature reviews, most recently through March 12, 2015.

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 the question of whether patients given assay-guided therapy or empiric therapy have different outcomes. To determine whether assay-guided treatment results in overall different outcomes than empiric treatment, it is important to take into account response rates, survival, adverse effects, and quality of life. These effects may be assessed indirectly, for example, using decision analysis, or directly with comparative trials. Both the 2002 BCBSA TEC Assessment and the 2004 systematic review recommend validating chemotherapy sensitivity and resistance assays with direct evidence gathered from prospective trials comparing patients treated empirically to patients treated with assay-directed therapy. In this way, not only can response rates and survival be taken into account, but also adverse events (e.g., from the toxic effects of an ineffective drug or delay or loss of benefits of an effective drug) and quality of life

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 low probability of response. The 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 with chemoresistance assays to those managed with 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 regarding EDR assays have focused on correlational studies that correlate results from predictive in vitro assays with observed outcomes of chemotherapy. However, in these studies, the 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, chemotherapy options, and probabilities of response. This process is problematic since 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, quality of life, 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 the

assay results or the accuracy of its predication for response. Examples of some of the earlier published correlation studies of the EDR assay include those by Eltabbakh and colleagues, Mehta et al, Holloway and co-workers, and Ellis et al.

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

Correlational Studies

Prospective

A study by Tiersten et al was designed to use the Oncotech EDR assay (Exiqon Diagnostics, Tustin, CA) to examine whether chemotherapy resistance was an independent predictor of progression free survival (PFS) in patients with ovarian cancer treated with neoadjuvant chemotherapy and surgical cytoreduction followed by intraperitoneal chemotherapy. Fifty-eight eligible women were prospectively enrolled on this study; however, results from the EDR assay were not used to direct therapy. Evaluable EDR assay results were available for 22 of the 58 patients. No difference in progression-free survival was reported. Follow-up has not been sufficient to measure overall survival. These data do not provide support for use of the EDR assay in predicting outcome and guiding patient management.

A 2006 review published by Nagoury et al included 21 non-comparative studies using ex-vivo programmed cell death assays. The authors of these studies correlated the drug susceptibility findings of the ex-vivo assay with objective clinical response (complete or partial) compared to non-responders for 659 total patients. The authors obtained aggregate positive values by 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 found to be eligible for inclusion and were tested with the EVA/PCD™ assay to determine which chemotherapeutic drugs to use. A further ten patients were excluded (five due to insufficient cellular yield, three for resistance to all drugs tested, and two due to physician's choice) yielding only 31 patients who received the assay-recommended treatment. The authors compared the results of these 31 patients treated with assay-directed chemotherapy to historic controls (not described) on the outcome of observed objective response rate (complete response and partial response). The objective response rate for the study was 64.5% (95% confidence interval [CI]: 46.9-78.9%) which was significantly greater than the stated historic standard of 30% objective response ($p<0.0001$).

Retrospective

In 2010, Matsuo et al published a study examining the relevance of EDR 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

(four platinum- or taxane-based) and secondary drugs (e.g., gemcitabine, topotecan, doxorubicin, etoposide, and 5-FU). Paclitaxel showed the highest resistance rate. Other agents had a resistance rate of less than 20%. There was only one (0.4%) tumor that 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. The investigator acknowledges that the study, due to its retrospective and non-comparative design is not sufficiently strong to validate use of this assay in managing therapy. Potential confounding factors, as described by the investigator, may have included tumor heterogeneity and the variations in resistance between primary tumor and metastases.

Another study by the same group evaluated the role of the EDR assay to platinum- and taxane-based therapies for management of 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 (LDR), intermediate drug resistance (IDR), or extreme drug resistance (EDR). The 58 patients (33.5%) whose tumors had LDR to both platinum and taxane showed statistically improved progression-free survival and overall survival (OS) compared to the 115 patients (66.5%) who demonstrated IDR or EDR to platinum and/or taxane (five-year OS rates, 41.1% vs. 30.9%, p=0.014). The five-year overall survival rates for the 28 (16.2%) cases that had optimal cytoreduction with LDR to both platinum and taxane was significantly improved over the 62 (35.8%) cases that were suboptimally cytoreduced with IDR or EDR to platinum and/or taxane (54.1% vs. 20.4%, respectively, p<0.001). Although the EDR assay was predictive for survival, it is of interest that assay results did not indicate response to therapy with either taxane or cisplatin. The investigators conclude that the EDR assay may be an independent predictor of progression free survival and overall survival; however, a prospective, randomized trial would be required to further assess its clinical utility in predicting response to taxane or platinum therapies.

A smaller study by Matsuo et al testing the EDR assay for prediction of uterine carcinosarcoma response to taxane and platinum was also conducted. Of 51 cases, 31 (60.8%) 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 chemotherapy cases was 70.6%. Presence of EDR to either platinum or taxane showed a significantly lower PFS (one-year PFS rate, 28.6% vs. 100%, p=0.01) and lower OS (five-year OS rate, 26.9% vs. 57.1%, p=0.033). These data 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 clinical trials would be required to validate use of this assay for directing chemotherapy regimens.

Matsuo et al also completed a study examining the rates of EDR after cytoreductive therapy and neoadjuvant chemotherapy versus the rates of ERD 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 conducted a retrospective review of 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 endpoints were time to progression (TTP), OS, and survival after recurrence (RS). The patient population was heterogeneous, with a median age of 59 years (range 24 to 89), tumor completely resected in 30% of patients, and varying tumor stages (Federation of Gynecologists and Obstetricians [FIGO] 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 independently predict patient outcomes regardless of whether the assay was performed at the time of the primary surgery or at recurrence

Hetland et al conducted a study to identify primary platinum resistance in epithelial ovarian cancer patients with FIGO Stage III-IV disease. Eighty-five biopsies from 58 patients were included in the study. 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 the 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 two drugs. Platinum resistance, as defined by the risk index, was associated with significantly poorer PFS (p=0.03) with a median value of 3.9 months (95% CI: 3.2 to 4.7) compared with the platinum sensitive group with a median PFS of 8.1 months (95% CI: 3.7 to 12.4). Patients who had partial response, stable disease or progressive disease were more resistant to platinum based on risk index score than those with a complete response (p=0.02). In a sub-group analysis of metastatic tumors, platinum resistance was not associated with PFS or clinical response. Response to paclitaxel or carboplatin/paclitaxel was not associated with PFS or clinical response. In vitro response was not associated with overall survival in any group.

Comparative Studies Testing Outcome with Assay-Directed Therapy versus Physician Chosen Therapy

None identified.

Section Summary

Some retrospective and prospective studies suggest 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 compare outcomes between 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, quality of life and adverse events, between assay-directed therapy and physician-directed therapy, with outcomes 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 (PPVs) 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 versus physician directed therapy. Relevant outcomes would include overall and disease-specific survival, as well as quality of life and adverse events.

The 2002 TEC Assessment and 2004 systematic review identified nine comparative studies, two of which were randomized. These authors reported that significant advantages for assay-guided therapy in terms of 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.

Comparative Studies Testing Outcome with Assay-Directed Therapy versus Physician-Chosen Therapy

In a case-control study, Moon et al retrospectively compared adenosine triphosphate (ATP) assay-based guided chemotherapy with empirical chemotherapy in unresectable non-small-cell lung cancer. All of the 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 endpoint was clinical response rate, assessed every two cycles of chemotherapy by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The secondary endpoints were PFS and OS. The response rate and survival in both groups were not statistically different. The platinum-sensitive subgroup by ATP assay showed a higher response rate than the empirical group (71% vs. 38%, respectively; p=0.02), but there was no statistical significance between PFS or OS.

In a small nonrandomized comparative study (n=64), Iwahashi et al reported on outcomes of chemosensitivity-guided chemotherapy (CSC) compared to standard chemotherapy and no chemotherapy in patients with advanced gastric cancer. In some subsets, survival was improved in the CSC subgroup. However, given the small sample, additional studies are needed to confirm these findings and to extend them to other malignancies.

Cree et al reported on a prospective, randomized trial of chemosensitivity assay-directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer. The primary aim of this randomized trial was to determine response rate and progression-free survival following chemotherapy in patients who had been treated according to an adenosine triphosphate (ATP)-based tumor chemosensitivity assay in comparison with the physician's choice. A total of 180 patients were randomized to assay-directed therapy (n=94) or physician-

choice chemotherapy (n=86). Median follow-up at analysis was 18 months; 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 progression-free survival of 93 days in the physician's-choice group and 104 days in the assay-directed group (hazard ratio 0.8, not significant). No difference was seen in overall survival between the groups, although 12 of 39 patients (41%) who crossed over from the physician's-choice arm obtained a response. Increased use of combination therapy was seen in the physician's-choice arm during the study as a result of the observed effects of assay-directed therapy in patients. The authors concluded that this small randomized, clinical trial documented a trend toward improved response and progression-free survival 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 remains an investigational method in this condition.

Correlational Studies

Prospective

Kim et al reported 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 endpoint of the study was to assess accuracy of the ATP-assay results, and the secondary endpoint 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 (WHO) criteria using a computed tomography (CT) scan after every two cycles of chemotherapy. Both 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% confidence interval [CI]: 77.2-99.9%), sensitivity 46.2% (95% CI: 19.2-74.9%), PPV 85.7% (95% CI: 42.1-99.6%) and NPV was 75.9% (95% CI: 55.1-89.3%). Median PFS was 4.2 months (95% CI: 3.4-5.0) and median OS was 11.8 months (95% CI: 9.7-13.8). The in vitro chemosensitive group showed a higher response rate (85.7% vs. 24.1%, respectively; p=0.005) compared to the chemoresistant group. 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.

In a European study, Ugurel et al reported on a nonrandomized, prospective, Phase II study of 53 evaluable patients with metastatic melanoma. All 53 received assay-directed therapy. This study found a 36% response rate in patients with chemosensitive tumors compared with 16% in those with chemoresistant tumors. Based on these preliminary results, a Phase III study is to follow.

Rutherford et al reported results from a prospective, noninterventional, multicenter cohort study that was designed to assess whether the ChemoFX assay was predictive of outcomes among women with histologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Three hundred thirty five patients were enrolled and treated with one of 15

study protocols, with treating physicians blinded to the ChemoFX assay result. Two hundred sixty-two patients (78.2% of total) 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 progression-free survival of median 8.8 months, compared with 5.9 months for those with assay-intermediate or –resistant regimens (HR 0.67, P=0.009). Mean overall survival was 37.5 months for patients treated with an assay-sensitive regimen, compared with 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 evaluated the ChemoFX's ability to 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 one 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 (95% range, 0.66 to 0.99), which the authors suggest indicates that patients with a mismatch had less benefit when treated with an assay-sensitive therapy.

Strengths of this study include its prospective design with physicians blinded to the assay results, which reduces the risk of bias in patient selection or measurement of outcomes. However, since the selection of chemotherapeutic agent was, by design, not influenced by the ChemoFX assay, the impact on health outcomes cannot be determined.

Krivak et al reported 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/taxane regimen. A total of 462 patients were enrolled, with 276 evaluable for inclusion in the 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 compared with nonresistant patients (HR=1.87; 95% CI, 1.29 to 2.70; p<0.001).

In a similar study design, Salom et al conducted a prospective, noninterventional, multicenter cohort study to assess whether the Microculture Kinetic (MiCK) assay (now called the CorrectChemo assay) 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 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 their treating physicians, who were blinded to the MiCK assay results. Overall survival Stage III or IV disease was longer if patients received a chemotherapy which was considered "best" by the MiCK assay, compared to shorter survival in patients who received a chemotherapy that was not the best. (HR 0.23, P < 0.01).

Jung et al conducted a single-center prospective study to determine whether sensitivity to paclitaxel and carboplatin, determined used the Histoculture Drug Resistance Assay (HDRA), was predictive of outcomes among women with advanced epithelial ovarian cancer. The study included 104 patients with epithelial ovarian cancer, all of whom had undergone initial surgery and were treated with paclitaxel and carboplatin therapy. Tumor cells' sensitivity to the chemotherapy agents was classified as sensitive, intermediate, or resistant to paclitaxel, carboplatin, or both, based on the HDRA. Patients whose tumors were sensitive to both drugs had a lower recurrence rate than those who had resistance to both drugs (29.2% vs 69.8%, P=0.02) and had a longer progression free survival (35 months vs 16 months, P=0.025).

While these studies establish that the results of chemosensitivity assays are correlated with outcome, they do not evaluate how the test may alter clinical decision-making and whether changes in management based on the test improve outcomes.

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

Gallion et al conducted a retrospective study that evaluated the association of ChemoFX test results with the treatment response of 256 patients with ovarian or peritoneal cancer who had been treated with at least one 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 nor were they calculable. For the subset of 135, in a multivariable analysis, ChemoFX was an independent significant predictor (p=0.006) of PFS along with two other clinical variables. Hazard ratio (HR) for resistant versus sensitive was 2.9 (95% CI: 1.4–6.30) and was 1.7 (95% CI: 1.2–2.5) for resistant versus intermediate. The median progression-free interval was nine months for the resistant group, 14 months for the intermediate group, and had not been achieved for the sensitive group.

Herzog et al included 147 patients from the above study by Gallion et al and reported on a total of 192 women with advanced-stage primary ovarian cancer, 175 of whom had tumors that were 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: 0.50-0.97). The authors concluded that the result of chemosensitivity testing with a drug response marker for therapy was predictive of OS in patients with primary ovarian cancer.

In a smaller study, Grigsby et al conducted a retrospective analysis to assess the association of pretreatment chemosensitivity to cisplatin with clinical outcomes among 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 to 58% for those with nonresponsive tumors (P=0.036).

Lee et al conducted a retrospective study of the histoculture drug response assays (HDRA) 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 in cisplatin (34.7%), the traditional drug used to treat epithelial ovarian cancer. A subset of 37 patients with FIGO Stage II/IV stage III or IV epithelial ovarian serous adenocarcinoma who had been treated with at least three cycles of carboplatin chemotherapy was assessed to compare outcomes between carboplatin-sensitive and -resistant patients. Multiple comparison and regression analyses established a cut-off value of 40% inhibition rate in response to 50 ug/mL carboplatin to determine sensitivity or resistance. This selected cut-off had a disease-free survival of 23.2 months (95% CI: 6.3-55.3) and 13.8 months (95% CI: 4.9-35.6) in the carboplatin-sensitive and carboplatin- resistant groups respectively ($p<0.05$). Overall survival between the two groups did not differ significantly, with carboplatin-sensitive patients having a mean 60.4 months and carboplatin-resistant patients having 37.3 months (p=0.621).

Strickland et al conducted a retrospective evaluation of the association between chemosensitivity to anthracyclines, measured by the drug-induced apoptosis MiCK assay (now called the CorrectChemo 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 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 non-responder. Patients determined to be chemoresponders to idarubicin were more likely to have complete response to chemotherapy (72%) than those who were non-responders (P=0.01). Data for the patient cohort were collected over a 14 year period from 1996-2010, which may limit the generalizability of the results to currently-used chemotherapy regimens. In addition, the MiCK assay is limited by lack of standardized cutoffs to discriminate responders from nonresponders.

Other retrospective studies have evaluated the association between chemosensitivity as measured by other assay types. Von Heideman et al evaluated the semi-automated fluorometric microculture cytotoxicity assay (FMCA) 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 non-responding patients.

Section Summary

The most direct evidence related to the effectiveness of chemosensitivity assays in the management of patients with cancer comes from several studies which compare outcomes for patients managed with an ATP-based tumor chemosensitivity assay with those managed with standard care, including one 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, suggest 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
There are only a few comparative studies that evaluate use of a chemosensitivity assay to select chemotherapy versus standard care, and these studies do not report significant differences in outcomes between groups. A larger number of studies have used correlational designs that evaluate the association between assay results and already known patient outcomes. These studies report that results of chemosensitivity and chemoresistance assays are predictive of outcomes. However, these studies do not evaluate whether these assays lead changes in management, and whether any changes in management lead to improved outcomes. In addition, interpretation of these studies is limited by heterogeneity in test methodology, tumor type, patient population, and chemotherapeutic agents. As a result, the clinical utility of chemoresistance and chemosensitivity assays has not been determined, and data are insufficient to determine whether use of the test to select chemotherapy regimens for individual patients will improve outcomes. Therefore, this testing is considered investigational.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines
The 2015 NCCN guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (v 3.2014) states the following, "chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions. The current level of evidence (category 3) is not sufficient to supplant standard-of-care chemotherapy.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update on the Use of Chemotherapy Sensitivity and Resistance Assays, 2011 also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.

U.S. Preventive Services Task Force Recommendations
Not Applicable.

Key Words:
Chemoresistance assays, chemosensitivity assays, drug sensitive, drug resistant, chemotherapy, drug sensitivity testing (DST), Thymidine Incorporation Assay, MTT, ATP-Cell Viability Assay, Differential Staining Cytotoxicity (DiSC) Assay, ChemoFx® Assay, Extreme Drug Resistance Assay (EDR), and Histoculture Drug Response Assay (HDRA), Oncotech, CorrectChemo® assay.

Approved by Governing Bodies:
Commercially available chemosensitivity and chemoresistance assays are laboratory developed tests for which approval from the U.S. Food and Drug Administration (FDA) is not required when the tests are performed in a laboratory licensed by the Clinical Laboratory Improvement

Act (CLIA) for high-complexity testing. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT coding:

86849	Unlisted immunology procedure
89240	Unlisted miscellaneous pathology test

The extreme drug resistance assay is a multistep laboratory procedure that might be identified by the following CPT codes:

87230	Toxin or antitoxin assay, tissue culture
88104	Cytopathology, fluids, washings or brushings; except cervical or vaginal; smears with interpretation
88305	Level IV surgical pathology, gross and microscopic examination
88313	Special stains including interpretation and report; Group II all other (e.g., iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry
88358	Morphometric analysis; tumor
89050	Cell count, miscellaneous body fluids

Effective January 1, 2016, there will be specific CPT codes for ChemoFX®

81535	Oncology (gynecologic), liver tumor cell culture and chemotherapeutic response by DAPI stand and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination (**Effective 01/01/16**)
81536	each additional single drug or drug combination (List separately in addition to code for primary procedure) (**Effective 01/01/16)**

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