### Prior Authorization Review
#### Panel MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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**Type of Submission – Check all that apply:**
- [ ] New Policy
- [X] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy **must** be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0245 Tumor Chemosensitivity Assays**

Clinical content was last revised 05/17/2016. Additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

**Revision and Update History since last PARP submission:**
- 06/08/2018 - This CPB has been updated with an additional reference.
- 01/24/2019 – Next tentative scheduled review date by Corporate.

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[www.aetnabetterhealth.com/pennsylvania](http://www.aetnabetterhealth.com/pennsylvania)  
Updated 06/08/2018
Tumor Chemosensitivity Assays

Number: 0245

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Policy

Aetna considers chemosensitivity assays (e.g., the ChemoFx assay, the differential staining cytotoxicity (DiSC) assay, the fluorescence (Cytoprint) assay, the human tumor cloning assay (HTCA), the human tumor stem cell assay, the methyl thiazolyl-diphenyl-tetrazolium bromide (MTT) assay, and the microculture kinetic (MiCK) apoptosis assay (also known as CorrectChemo)) experimental and investigational because there is insufficient evidence that these assays influence management decisions such that clinical outcomes are improved.

See

CPB 0758 - Tumor Chemoresistance Assays

Aetna considers chemosensitivity assays (e.g., the ChemoFx assay, the differential staining cytotoxicity (DiSC) assay, the fluorescence (Cytoprint) assay, the human tumor cloning assay (HTCA), the human tumor stem cell assay, the methyl thiazolyl-diphenyl-tetrazolium bromide (MTT) assay, and the microculture kinetic (MiCK) apoptosis assay (also known as CorrectChemo)) experimental and investigational because there is insufficient evidence that these assays influence management decisions such that clinical outcomes are improved.

Additioal Information

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CPB 0758 - Tumor Chemoresistance Assays

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Chemosensitivity assays are intended to predict the sensitivity of various tumors to chemotherapeutic agents, with the intent of identifying more effective treatment protocols which would then translate into improved clinical survival. By contrast, tumor chemoresistance assays are focused on identifying resistant drugs. The focus of this policy is on tumor chemosensitivity assays.

A variety of sensitivity assays have been developed, which differ in their processing, and the technique used to measure sensitivity. All techniques involve 4 basic steps: (i) isolation of cells; (ii) incubation of cells with drugs; (iii) assessment of cell survival; and (iv) interpretation of the result. There have been no prospective clinical trials that have demonstrated that there is an improved survival among patients in whom chemosensitivity assays were used to positively select chemotherapy regimens.

Although numerous attempts have been made to analyze the effects of drugs on cell metabolism, cell morphology, radionuclide incorporation, and various aspects of cell membrane integrity, there is no consensus that these assays can be utilized routinely in the clinical setting. Major questions remain unanswered, such as how best to select patients who benefit from these tests and whether patients receiving assay-selected chemotherapy show better response than those receiving best current therapy.

Based on a review of the current literature, the American Society of Clinical Oncology (ASCO) Working Group found insufficient evidence to support the use of any chemotherapy sensitivity and resistance assays (CSRAs) in oncological practice. Specifically, the ASCO Work Group found limitations in the literature that included small sample sizes and a lack of prospective studies. For technically challenging CSRAs that require colony formation (e.g., the human tumor cloning assay), and for surgical procedures including the sub-renal
capsule assay, the success rate of the CSRAs is modest. Furthermore, preparation of the assay may involve complex laboratory work, limiting a broad application of the technology to routine clinical practice. Because the in-vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority (Schrag et al, 2004).

In a prospective, randomized controlled study, Cree and colleagues (2007) ascertained response rate and progression-free survival (PFS) following chemotherapy in patients with platinum-resistant recurrent ovarian cancer, who had been treated according to an adenosine triphosphate (ATP) bioluminescence-based tumor chemosensitivity assay in comparison with physician's choice. A total of 180 patients were randomized to assay-directed therapy (n = 94) or physician's-choice chemotherapy (n = 86). Median follow-up at analysis was 18 months. Response was assessable in 147 patients: 31.5 % achieved a partial or complete response in the physician's-choice group compared with 40.5 % in the assay-directed group (26 versus 31 % by intention-to-treat analysis respectively). Intention-to-treat analysis showed a median PFS of 93 days in the physician's-choice group and 104 days in the assay-directed group (hazard ratio [HR] 0.8, 95 % confidence interval [CI]: 0.59 to 1.10, not significant). No difference was seen in overall survival (OS) between the groups, although 12/39 (41 %) of patients who crossed-over from the physician's-choice arm obtained a response.

Increased use of combination therapy was seen in the physician's-choice arm during the study as a result of the observed effects of assay-directed therapy in patients. Patients entering the physician's-choice arm of the study during the first year did significantly worse than those who entered in the subsequent years (HR 0.44, 95 % CI: 0.2 to 0.9, p < 0.03). The authors concluded that the findings of this small randomized clinical trial has documented a trend towards improved response and PFS for assay-directed treatment. Chemosensitivity testing might provide useful
information in some patients with ovarian cancer, although a larger trial is required to confirm this. They noted that the ATP-based tumor chemosensitivity assay remains an investigational method in this condition.

In a systematic review and meta-analysis on the use of microsatellite instability (MSI) in predicting the effectiveness of chemotherapy in metastatic colorectal cancer (CRC), Des Guetz et al (2009) stated that MSI status is a good prognostic factor for CRC; but its predictive value for chemosensitivity remains controversial. Studies were identified by electronic search through PubMed, Embase and ASCO proceedings online databases, using several key words (colorectal cancer, chemotherapy, microsatellite instability). For each study, the ratio of response rate (RR), complete response (CR) and partial response (PR) divided by stable disease and progression was calculated. From a total of 190 articles and 100 abstracts, only 8 independent studies were selected. The data were analysed with a random-effect model (due to heterogeneity between studies) using EasyMA software. Statistical calculations were performed on 6 studies representing 964 patients (mean age of 63 years; 91 MSI-high; 873 microsatellite stable (MSS) tumors). A total of 287 patients received 5-fluorouracil (5FU)-based chemotherapy, whereas 678 patients received combinations of 5FU or capecitabine with oxaliplatin and/or irinotecan. No benefit of metastatic chemotherapy in terms of RR for MSI-high patients compared with MSS patients was found. The global HR for RR was 0.82 (95% CI: 0.65 to 1.03; p = 0.09). The authors concluded that MSI status does not predict the effect of chemotherapy, which is similar in MSI-high and MSS metastatic CRC tumors.

Kim and colleagues (2010) determined the most accurate analytic method to define in vitro chemosensitivity, using clinical response as reference standard in prospective clinical trial, and ascertained accuracy of adenosine triphosphate-based chemotherapy response assay (ATP-CRA). A total of
48 patients with chemo-naïve, histologically confirmed, locally advanced or metastatic gastric cancer were enrolled for the study and were treated with combination chemotherapy of paclitaxel 175 mg/m\(^2\) and cisplatin 75 mg/m\(^2\) for maximum of 6 cycles after obtaining specimen for ATP-CRA. These researchers performed the receiver operator characteristic (ROC) curve analysis using patient responses by World Health Organization criteria and ATP-CRA results to define the method with the highest accuracy. Median PFS was 4.2 months (95 % CI: 3.4 to 5.0) and median OS was 11.8 months (95 % CI: 9.7 to 13.8) for all enrolled patients. Chemosensitivity index method yielded highest accuracy of 77.8 % by ROC curve analysis, and the specificity, sensitivity, positive and negative predictive values were 95.7 %, 46.2 %, 85.7 %, and 75.9 %, respectively. In-vitro chemosensitive group showed higher response rate (85.7 % versus 24.1 %) (\(p = 0.005\)) compared to chemoresistant group. The authors concluded that ATP-CRA could predict clinical response to paclitaxel and cisplatin chemotherapy with high accuracy in advanced gastric cancer patients. They stated that these findings support the use of ATP-CRA in further validation studies.

Schink and Copeland (2011) stated that in this era of personalized medicine, patients with recurrent ovarian cancer deserve better than the 25 % response rate that is associated with drugs selected based on clinical information alone. In the past decade, marked laboratory improvements have enabled chemosensitivity assay testing to yield a 0.70 correlation with response, and to accurately predict PFS and OS. Compelling retrospective data supporting the use of this technology can not be ignored while waiting for a co-operative group to test whether chemosensitivity assay should be used to direct salvage therapy. In contrast, Markman (2011) stated that unfortunately, no reliable evidence-based data have shown any in-vitro chemosensitivity assay strategy to be clinically useful in the management of recurrent ovarian cancer, despite
frequent use. Several clinical trials have been proposed with the potential to support or refute the relevance of these approaches.

Huh et al (2011) examined the patterns of in-vitro tumor response rates as determined by ChemoFx are consistent with expected population response rates. A total of 923 tumor specimens from patients with high-risk early-stage, advanced stage, or recurrent endometrial cancer were sent for testing with the ChemoFx drug response marker from August 2, 2006, to August 31, 2009. Tumors were categorized as responsive (R), intermediately responsive (IR), or non-responsive (NR) to each drug or combination tested. Response rates from clinical trials were identified and compared with the corresponding in vitro response rates. Of the 923 specimens received, 759 (82 %) were successfully tested by ChemoFx. Of these, 755 were tested for at least 1 of 5 National Comprehensive Cancer Network-recommended endometrial cancer drugs. The response rates (R+IR) for these drugs were as follows: 66 % carboplatin-paclitaxel, 48 % carboplatin, 37 % cisplatin, 23 % doxorubicin, and 36 % paclitaxel. Moreover, 20 % of tumors were pan-sensitive (R or IR) to all 5 regimens tested, 27 % were pan-resistant (NR), and 53 % showed different degrees of response to different drugs. The authors concluded that ChemoFx in-vitro response rates were consistent with published population response rates, and the ChemoFx drug response marker may provide clinically useful information to better optimize individual chemotherapy for treatment of women with endometrial cancer.

Burstein et al (2011) updated the ASCO Technology Assessment guidelines on CSRAs published in 2004. An Update Working Group reviewed data published between December 1, 2003, and May 31, 2010. Medline and the Cochrane Library were searched yielding 11,313 new articles. The limits for "human and English" were used, and then standard ASCO search strings for randomized controlled trials (RCTs), meta-analyses, guidelines, and reviews were added,
yielding 1,298 articles for abstract review. Of these, only 21 articles met pre-defined inclusion criteria and underwent full text review, and 5 reports of RCTs were included for data extraction. Review of the literature does not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice. The authors concluded that the use of CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. They noted that oncologists should make chemotherapy treatment recommendations based on published reports of clinical trials and a patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.

The in-vitro microculture kinetic (MiCK) assay, a drug-induced apoptosis assay, has been used to predict single or combination chemotherapy response in leukemia patients. In the MiCK apoptosis assay, the extent of apoptosis is reported in kinetic units (KU), which are determined by the slope of the curve created when optical density caused by cell blebbing is plotted as a function of time (Kravtsov et al, 1998).

In a feasibility study, Ballard et al (2010) examined the use of the MiCK apoptosis assay in endometrial cancer specimens. Endometrial cancer specimens from total abdominal hysterectomies were processed at a central laboratory. Single cell suspensions of viable endometrial cancer cells were plated in individual wells. Single and combination regimens were tested: combinations of doxorubicin, cisplatin, and paclitaxel and carboplatin and paclitaxel (Gynecologic Oncology Group [GOG] 209 endometrial cancer phase III trial arms) as well as single-agent testing with paclitaxel, carboplatin, doxorubicin, cisplatin, ifosfamide, and vincristine (active agents in GOG trials). Apoptosis was measured continuously over 48 hours. Fifteen of 19 patients had successful assays. The highest mean chemo sensitivity was noted in the combination of cisplatin, doxorubicin, and
paclitaxel with lower mean chemosensitivity for carboplatin and paclitaxel. Combination chemotherapy had higher chemosensitivity than single-drug chemotherapy. However, in 25% of patients a single-drug had higher chemosensitivity than combination chemotherapy. As single agents, ifosfamide, cisplatin, and paclitaxel had the highest kinetic unit values.

The authors concluded that using a panel of agents simulating clinical dose regimens, the MiCK apoptosis assay was feasible in evaluating in-vitro chemosensitivity of endometrial cancer. The MiCK apoptosis assay results correlated with GOG clinical trial results. However, 25% of patients might be best treated with single-agent chemotherapy selected by the MiCK assay. Ifosfamide, cisplatin, and paclitaxel appear to have high activity as single agents. The authors stated that the MiCK apoptosis assay may be useful in future new drug testing and individualizing endometrial cancer patient's chemotherapy management.

Bosserman et al (2012) noted that blinded clinical trials have shown higher response rates and longer survival in groups of patients with acute myelocytic leukemia (AML) and epithelial ovarian cancer who have been treated with drugs that show high apoptosis in the MiCK apoptosis assay. Un-blinded clinical trials in multiple tumor types have shown that the assay will be used frequently by clinicians to determine treatment, and when used, results in higher response rates, longer times to relapse, and longer survivals. Model economic analyses suggest possible cost savings in clinical use based on increased generic drug use and single-agent substitution for combination therapies; 2 initial studies with drugs in development are promising. The authors concluded that the MiCK apoptosis assay may help reduce costs and speed time to drug approval; correlative studies with molecular biomarkers are planned. They stated that this assay may have a role both in personalized clinical therapy and in more efficient drug development.
In a prospective, multi-institutional and blinded trial, Salom et al (2012) examined if the MiCK apoptosis assay could predict the best therapy for patients with ovarian cancer. The MiCK assay was performed in 104 evaluable ovarian cancer patients treated with chemotherapy. The assay was performed prior to therapy, but treating physicians were not told of the results and selected treatment only on clinical criteria. Outcomes (response, time to relapse, and survival) were compared to the drug-induced apoptosis observed in the assay. Overall survival in primary therapy, chemotherapy naïve patients with stage III or IV disease was longer if patients received a chemotherapy that was best in the MiCK assay, compared to shorter survival in patients who received a chemotherapy that was not the best (p < 0.01, hazard ratio HR 0.23). Multivariate model risk ratio showed use of the best chemotherapy in the MiCK assay was the strongest predictor of overall survival (p < 0.01) in stage III or IV patients. Standard therapy with carboplatin plus paclitaxel (C + P) was not the best chemotherapy in the MiCK assay in 44 % of patients. If patients received C + P and it was the best chemotherapy in the MiCK assay, they had longer survival than those patients receiving C + P when it was not the best chemotherapy in the assay (p = 0.03). Relapse-free interval in primary therapy patients was longer if patients received the best chemotherapy from the MiCK assay (p = 0.03, HR 0.52). Response rates (CR + PR) were higher if physicians used an active chemotherapy based on the MiCK assay (p = 0.03). The authors concluded that the MiCK apoptosis assay can predict the chemotherapy associated with better outcomes in ovarian cancer patients. They stated that this study quantified outcome benefits on which a prospective, randomized trial can be developed.

Strickland et al (2013) examined if the level of drug-induced apoptosis (chemosensitivity) demonstrated by the MiCK assay significantly predicted outcomes after standard AML induction therapy. A total of 109 patients with untreated AML had blood and/or bone marrow aspirate samples analyzed for
anthracycline-induced apoptosis using the MiCK assay. The amount of apoptosis observed over 48 hrs was determined and expressed as KU of apoptosis. Complete remission (CR) was significantly higher (72 %) in patients with high idarubicin-induced apoptosis greater than 3 KU compared to patients with apoptosis less than or equal to 3 KU (p = 0.01). Multi-variate analysis showed the only significant variables to be idarubicin-induced apoptosis and karyotype. Median overall survival of patients with idarubicin-induced apoptosis greater than 3 KU was 16.1 months compared to 4.5 months in patients with apoptosis less than or equal to 3 KU (p = 0.004). Multi-variate analysis showed the only significant variable to be idarubicin-induced apoptosis. The authors concluded that chemotherapy-induced apoptosis measured by the MiCK assay demonstrated significant correlation with outcomes and appeared predictive of complete remission and overall survival for patients receiving standard induction chemotherapy.

There is currently insufficient evidence that the use of the MiCK apoptosis assay improves survival of cancer patients. Well-designed studies are needed to ascertain clinical value of the MiCK apoptosis assay.

Bellamy (1992) stated that cancer chemotherapy has witnessed a great deal of progress since the introduction of the nitrogen mustards in the 1940s. Unfortunately, individual patients with apparently identical tumor histologies do not always respond identically to the same drug regimen. Determining the sensitivity and resistance of an organism before treatment has been the standard of care in infectious diseases for many years, while in oncology treatment has been initiated according to tumor histology rather than the tumor's sensitivity to a given agent. Attempts to individualize therapy have been the goal of oncologists since the 1950s. Since that time a number of in-vitro assays have been developed to predict therapeutic outcome prior to the start of therapy. In the 1970s, with the introduction of the human tumor stem cell assay, it was generally believed that oncology
was on the threshold of entering an era of predictive in-vitro chemosensitivity testing. Unfortunately, this assay was shown to have a number of technical drawbacks including the low plating efficiencies of many primary tumor samples, which thus limited the percentage that can be evaluated, leaving clinicians still at this threshold today. Several recent developments, such as the Kern assay, which measures inhibition of radioactive precursors into tumor cells in the presence of antineoplastic agents, ATP bioluminescence assays, and the fluorescent Cytoprint assay offer the promise of rapid and sensitive results. Other assays, such as the tetrazolium-based MTT and the sulphorhodamine blue assay appear to hold more promise in the screening and evaluation of potential new agents in established tumor cell lines than for evaluating chemosensitivity of clinical specimens. However, before a particular assay can be considered as an in-vitro test of chemosensitivity or resistance, controlled prospective studies must be carried out to validate the assay in a number of different tumor types.

Tavassoli et al (1995) noted that in-vitro chemosensitivity assays (IVCAs) are expensive laboratory tests utilized to assist oncologists in the selection of chemotherapeutic regimens. Their utility is disputed; yet, these assays continue to be requested because of the importance of the information they can provide and their scientifically logical approach. Therefore, these researchers compared the results of 2 assays offered to clinicians at the authors’ hospital; the extreme drug resistance assay performed by Oncotech (OT) and the fluorescent Cytoprint assays performed by Analytical Biosystems (AB). The 2 techniques used and the expression of assay results by the 2 companies were discussed. A total of 20 neoplasms, all at least 3 cm in diameter and predominantly of breast and ovarian origin, were compared. Oncotech performed 74 drug assays on 17 tumors, while AB performed 194 assays on the corresponding neoplasms; 3 neoplasms were insufficient for comparison. Evaluation of the results revealed apparent disagreement on at least 44 drug assays
with complete disagreement on at least 2 of the drugs tested in 12 of 17 cases. The authors concluded that based on available information, comparisons between IVCAs showed great variation in results; moreover they stated that prospective studies are needed to evaluate commercially available assays for correlation with clinical outcome, and results should be expressed so comparisons can be readily made.

Recht et al (1998) stated that to individually tailor chemotherapy for patients with malignant gliomas according to tumor chemosensitivity, a rapid assay system that can be performed with a high success rate is needed. The fluorescent Cytoprint assay (FCA) can assess multiple chemotherapeutic agents using small (approximately 500 cells) tumor aggregates very quickly (approximately 1 week). Tissue samples from 51 patients with malignant gliomas obtained either at time of initial diagnosis (n = 34) or at recurrence were assayed using this method. The assay success rate approached 90 % in those culture samples that were histologically verified as tumor. A meaningful number of agents could be tested both on samples obtained by stereotactic biopsy (median of 5) and on specimens from more extensive resections (median of 6). A total of 193 FCAs were performed on a samples obtained from 36 patients. In only 26 assays (14 %) was an agent deemed sensitive (greater than 90 % cell kill) to a chemotherapeutic agent; 62 % of sensitive FCAs were observed in tumors tested against the activated analog of cyclophosphamide, 4-hydroxyperoxycyclophosphamide (4-HC), where a sensitivity rate (# samples sensitive/total tested against agent) of 64 % (95 % CI: 36.6 % to 77.9 %) was noted. This rate was significantly higher than with any other agent tested (p = 0.012, 2-sided McNemar's test) and was not affected by age, histology or disease status. The authors concluded that: (i) the FCA represents a feasible method for quickly assaying tumors for sensitivity to multiple chemotherapeutic agents;
and (ii) malignant gliomas may be particularly sensitive to 4-HC. The findings of this feasibility study need to be validated by well-designed studies.

In a prospective study, Rutherford et al (2013) evaluated the use of a chemoresponse assay in recurrent ovarian cancer patients. Women with persistent or recurrent ovarian cancer were enrolled under an IRB-approved protocol, and fresh tissue samples were collected for chemoresponse testing. Patients were treated with 1 of 15 protocol-designated treatments empirically selected by the oncologist, blinded to the assay results. Each treatment was classified by the assay as: (i) sensitive (S), (ii) intermediate (I), or (iii) resistant (R). Patients were prospectively monitored for PFS and OS. Associations of assay response for the physician-selected treatment with PFS and OS were analyzed. A total of 262 evaluable patients were enrolled. Patients treated with an assay-sensitive regimen demonstrated significantly improved PFS and OS while there was no difference in clinical outcomes between I and R groups. Median PFS was 8.8 months for S versus 5.9 months for I+R (HR = 0.67, p = 0.009). The association with assay response was consistent in both platinum-sensitive and platinum-resistant tumors (HR: 0.71 versus 0.66) and was independent of other covariates in multivariate analysis (HR = 0.66, p = 0.020). A statistically significant 14-month improvement in mean OS (37.5 months for S versus 23.9 months for I+R, HR = 0.61, p = 0.010) was demonstrated. The authors concluded that this prospective study demonstrated improved PFS and OS for patients with either platinum-sensitive or platinum-resistant recurrent ovarian cancer treated with assay-sensitive agents. Moreover, they stated that “ChemoFx, the chemoresponse assay employed in the current study, has been previously evaluated in retrospective studies inclusive of both primary and recurrent epithelial ovarian cancer (EOC). These promising results warranted further evaluation in the form of this current prospective, multi-site, non-interventional trial .... Furthermore,
the results suggest that effective (sensitive) treatment options could be available for many more patients than is currently achieved by empiric treatment. These compelling data suggest that it may be reasonable to prospectively utilize chemoresponse assays to assist clinicians in the optimal prioritization of therapy for both platinum-sensitive and platinum-resistant patients with recurrent EOC.

Grendys et al (2014) summarized recent scientific and medical literature regarding chemoresponse assays or chemotherapy sensitivity and resistance assays (CSRAs), specifically as applied to epithelial ovarian cancer. A total of 67 articles, identified through PubMed using the key words "in vitro chemoresponse assay", "chemo sensitivity resistance assay", "ATP", "HDRA", "EDR", "MiCK", and "ChemoFx" were reviewed. Recent publications on marker validation, including relevant clinical trial designs, were also included. Recent CSRA research and clinical studies were outlined in this review. Published findings demonstrated benefits regarding patient outcome with respect to recent CSRAs. Specifically, analytical and clinical validations, as well as clinical utility and economic benefit, of the most common clinically used CSRA in the United States support its use to aid in making effective, individualized clinical treatment selections for patients with ovarian cancer. Moreover, the authors stated that despite several years of chemoresponse assay development and clinical experience with these assays, studies have largely been confined to single-institutional, retrospective evaluations. Recent large, prospective, multi-site clinical studies that correlate ChemoFx assay results with OS and PFS in both primary and recurrent ovarian cancers indicated that the assay may offer significant clinical benefit for patients, is predictive of treatment outcomes, and is potentially economically beneficial by reducing the chance that ineffective chemotherapy is administered.

Krivak et al (2014) examined if a chemoresponse assay can identify patients who are platinum-resistant prior to treatment.
Women (n = 276) with International Federation of Gynecology and Obstetrics stage III-IV ovarian, fallopian, and peritoneal cancer were enrolled in an observational study, and the responsiveness of their tumors was evaluated using a chemoresponse assay (ChemoFx). All patients were treated with a platinum/taxane regimen following cytoreductive surgery. Assay responses to carboplatin or paclitaxel were classified as: (i) sensitive, (ii) intermediate sensitive (IS), or (iii) resistant. Association of assay response with PFS was analyzed using the Kaplan-Meier method and a Cox regression model. Patients whose tumors were resistant to carboplatin were at increased risk of disease progression compared to those with non-resistant (sensitive + IS) tumors (median PFS: 11.8 versus 16.6 months, respectively, p < 0.001), and the association was confirmed after adjusting for other clinical factors (HR, 1.71; 95 % CI: 1.12 to 2.62; p = .013). Association of assay response to paclitaxel with PFS trended in multi-variate analysis (HR, 1.28; 95 % CI: 0.84 to 1.95; p = 0.245). For tumors resistant to carboplatin, 59 % were sensitive or IS to at least 1 other commonly used agent, demonstrating the ability of the assay to inform treatment decisions beyond the standard platinum/taxane regimen. The authors concluded that assay resistance to carboplatin is strongly associated with shortened PFS among advanced-stage epithelial ovarian cancer patients treated with carboplatin + paclitaxel therapy, supporting use of this assay to identify patients likely to experience early recurrence on standard platinum-based therapy. They stated that the chemoresponse assay evaluated herein is independently associated with PFS and may be used to predict platinum resistance in patients with advanced-stage EOC prior to treatment. Patients predicted for poorer outcome (i.e., platinum resistance) by the assay (and in conjunction with other clinical factors) may be considered for investigation of alternate treatment options.
Tian et al (2014) stated that recently, a prospective study (Rutherford et al, 2013) reported improved clinical outcomes for recurrent ovarian cancer patients treated with chemotherapies indicated to be sensitive by a chemoresponse assay (ChemoFx), compared with those patients treated with non-sensitive therapies, thereby demonstrating the assay's prognostic properties. Due to cross-drug response over different treatments and possible association of in-vitro chemosensitivity of a tumor with its inherent biology, further analysis is required to ascertain whether the assay performs as a predictive marker as well. Women with persistent or recurrent EOC (n = 262) were empirically treated with 1 of 15 therapies, blinded to assay results. Each patient's tumor was assayed for responsiveness to the 15 therapies. The assay's ability to predict PFS was assessed by comparing the association when the assayed therapy matches the administered therapy (match) with the association when the assayed therapy is randomly selected; not necessarily matching the administered therapy (mismatch). Patients treated with assay-sensitive therapies had improved PFS versus patients treated with non-sensitive therapies, with the assay result for match significantly associated with PFS (HR = 0.67, 95 % CI: 0.50 to 0.91, p = 0.009). On the basis of 3,000 simulations, the mean HR for mismatch was 0.81 (95 % range = 0.66 to 0.99), with 3.4 % of HRs less than 0.67, indicating that HR for match is lower than for mismatch. While 47 % of tumors were non-sensitive to all assayed therapies and 9 % were sensitive to all, 44 % displayed heterogeneity in assay results. Improved outcome was associated with the administration of an assay-sensitive therapy, regardless of homogeneous or heterogeneous assay responses across all of the assayed therapies. The authors concluded that these analyses provided supportive evidence that this chemoresponse assay is a predictive marker, demonstrating its ability to discern specific therapies that are likely to be more effective among multiple alternatives. They stated that clinical validations for chemoresponse assays, which simultaneously assess multiple markers/therapies, must be carefully...
considered. Through further analysis of a prospective study and by using several analytical approaches, the current study further evaluated the clinical value of a chemoresponse assay. The results provided reasonable evidence that this assay is a predictive marker, with the capacity to discern specific therapies that are likely to be more effective, and women with recurrent EOC may benefit from assay-informed therapy selection.

Moreover, the National Comprehensive Cancer Network's clinical practice guideline on “Ovarian cancer” (Version 3.2014) states that “Chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; however, the current level of evidence (category 3) is not sufficient to supplant stand-of-care chemotherapy. Thus, the NCCN panel felt that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3) owing to the lack of demonstrable efficacy for such an approach. ASCO also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting”.

Tartar and colleagues (2016) stated that an alternative approach to the current therapy of ovarian carcinoma is the individualization of treatment by determining the sensitivity of tumoral tissue to chemotherapeutic agents before the initiation of chemotherapy. These researchers examined the effectiveness of in-vitro chemosensitivity assays in ovarian carcinoma and measured the correlation of 3 leading assays. Fresh tumoral tissue samples of 26 newly diagnosed primary ovarian cancer patients were studied with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, adenosine triphosphate-tumor chemosensitivity assay (ATP-TCA) and differential staining cytotoxicity (DISC) assays. Chemosensitivity of tumors were studied for paclitaxel,
carboplatin, docetaxel, topotecan, gemcitabine, and doxorubicin with each of the 3 assays. Subgroup analysis was performed for stage, grade, and histologic type. The in-vitro chemosensitivity results of MTT, ATP, and DISC assays were found to be similar. The subgroups in which in-vitro assays would be more useful were encountered for patients with advanced stage and serous histology ovarian carcinoma. The authors concluded that in-vitro chemosensitivity can be determined in ovarian carcinoma with ATP, MTT, or DISC assays before the initiation of chemotherapy; these 2 assays correlated well with each other and were particularly useful for serous and advanced cancers. Moreover, these investigators stated that large prospective randomized studies comparing standard versus assay-directed therapy with an end-point of OS are needed before routine clinical utilization of these assays.

Kwon and associates (2016) evaluated the usefulness of the in-vitro ATP-based chemotherapy response assay (ATP-CRA) for prediction of clinical response to fluorouracil-based adjuvant chemotherapy in stage II CRC. Tumor specimens of 86 patients with pathologically confirmed stage II colorectal adenocarcinoma were tested for chemosensitivity to fluorouracil. Chemosensitivity was determined by cell death rate (CDR) of drug-exposed cells, calculated by comparing the intracellular ATP level with that of untreated controls. Among the 86 enrolled patients who underwent radical surgery followed by fluorouracil-based adjuvant chemotherapy, recurrence was found in 11 patients (12.7 %). The CDR of greater than or equal to 20 % group was associated with better disease-free survival (DFS) than the CDR of less than 20 % group (89.4 % versus 70.1 %, p = 0.027). Multivariate analysis showed that CDR of less than 20 % and T4 stage were poor prognostic factors for DFS after fluorouracil-based adjuvant chemotherapy. The authors concluded that in-vitro ATP-CRA may be a useful assay for identifying patients who might benefit from fluorouracil-based adjuvant chemotherapy in stage II CRC. A major drawback of this study was the
threshold value of 20% CDR for defining chemotherapy-sensitive and -resistant groups. Previous studies have reported various threshold values for CDR, ranging from 30% to 50%. This discrepancy suggested the difficulty of the clinical application. Thus, these findings should be confirmed in independent patient cohorts.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>81535</td>
<td>Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination [ChemoFX assay]</td>
</tr>
<tr>
<td>81536</td>
<td>each additional single drug or drug combination (List separately in addition to code for primary procedure) [ChemoFX assay]</td>
</tr>
<tr>
<td>87230</td>
<td>Toxin or antitoxin assay, tissue culture (e.g., Clostridium difficile toxin)</td>
</tr>
<tr>
<td>88104</td>
<td>Cytopathology, fluids, washings or brushing, except cervical or vaginal; smears with interpretation</td>
</tr>
<tr>
<td>88305</td>
<td>Level IV surgical pathology, gross and microscopic examination</td>
</tr>
<tr>
<td>+ 88313</td>
<td>Special stains; Group II, all other (e.g., iron, trichrome), except immunocytochemistry and immunoperoxidase stains, each</td>
</tr>
<tr>
<td>88358</td>
<td>Morphometric analysis; tumor (e.g., DNA ploidy)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>89050</td>
<td>Cell count, miscellaneous body fluids (e.g., cerebrospinal fluid, joint fluid), except blood</td>
</tr>
</tbody>
</table>

Differential staining cytotoxicity (DiSC) assay:
No specific code

Human tumor cloning assay (HTCA):
No specific code

Human tumor stem cell assay:
No specific code

Methyl thiazolyl-diphenyl-tetrazolium bromide (MTT) assay:
No specific code

Microculture kinetic (MiCK) apoptosis assay (CorrectChemo):
No specific code

Cytoprint assay:
No specific code

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>88230</td>
<td>Tissue culture for non-neoplastic disorders; lymphocyte</td>
</tr>
<tr>
<td>88233</td>
<td>skin or other solid tissue biopsy</td>
</tr>
<tr>
<td>88235</td>
<td>amniotic fluid or chorionic villus cells</td>
</tr>
<tr>
<td>88237</td>
<td>Tissue culture for neoplastic disorders; bone marrow, blood cells</td>
</tr>
<tr>
<td>88239</td>
<td>solid tumor</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9000 - J9999</td>
<td>Chemotherapy drugs</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:
The above policy is based on the following references:


8. Cortazar P, Johnson BE. Review of the efficacy of individualized chemotherapy selected by in vitro drug


17. Kornmann M, Beger HG, Link KH. Chemosensitivity testing and test-directed chemotherapy in human


27. Quintieri L, Fantin M, Vizler C. Identification of molecular determinants of tumor sensitivity and

28. Kubota T, Weisenthal L. Chemotherapy sensitivity and resistance testing: To be 'standard' or to be individualized, that is the question. Gastric Cancer. 2006;9(2):82-87.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number:
0245 Tumor Chemosensitivity Assays

There are no amendments for Medicaid.