Medical Policy

***Current Policy Effective Date: 1/1/24**
(See policy history boxes for previous effective dates)

Title: Chemosensitivity and Chemoresistance Assay, In Vitro

Description/Background

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. Thus, 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.

Varieties of chemosensitivity and chemoresistance assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and non-viable 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. However, all assays require drug exposures ranging from several-fold below physiological relevance to several-fold above physiological relevance. Although varieties 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

Differential Staining Cytotoxicity Assay
The Differential Staining Cytotoxicity (DiSC) Assay involves mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation.[1] Cells are then established in culture and treated with the drugs of interest at 3 dose levels; the middle dose is that which could be achieved in therapy; 10-fold lower than the physiologically relevant dose; and 10-fold higher. Exposure time ranges from 4-6 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 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.

EVA/PCD Assay

The EVA/PCD™ assay (Rational Therapeutics) 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 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 micro-aggregates are believed to approximate the human tumor micro-environment more closely. 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 & Fast Green dye with glutaraldehyde-fixed avian erythrocytes are added to the cellular suspensions.[2] 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.[3]

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.[4] 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

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 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.[5]

Extreme Drug Resistance Assay

The Extreme Drug Resistance assay (EDR®)[6] (commercially available at Exiqon Diagnostics, Tustin, CA) 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. Small tissue samples are incubated with the drug(s) of interest for 5 days at doses ranging from 5-fold below to 80-fold above concentrations that would reflect physiological relevance. Subsequently, tritiated thymidine is added to the culture, 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 highly resistant when thymidine incorporation is at least 1 standard deviation (SD) above reference samples.

METHODS THAT QUANTIFY CELL VIABILITY USING COLORIMETRIC ASSAY

Histoculture Drug Resistance Assay
The Histoculture Drug Resistance Assay (HDRA), AntiCancer, Inc. (San Diego, CA).[7] This assay evaluates cell growth 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 CHEMOLUMINESCENT PRECURSORS BY MACROMOLECULES IN VIABLE CELLS

Adenosine Triphosphate (ATP) Bioluminescence Assay
The 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, 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 that the tumor is resistant to the agent of interest.

ChemoFx® Assay
ChemoFX® (Helomics, previously called Precision Therapeutics) assay also relies on quantifying ATP based on chemoluminescence.[8,9] Cells must be grown in a monolayer rather than in a 3- dimensional matrix.

Regulatory Status:

Commercially available chemosensitivity and chemoresistance assays are laboratory-developed tests for which approval from the U.S. Food and Drug Administration 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 CLIA.

Medical Policy Statement

Chemosensitivity and chemoresistance assays have not been scientifically demonstrated to be useful in selecting chemotherapy regimens for individual patients. There is insufficient evidence that chemosensitivity or chemoresistant assays improve patient outcomes. Use of these tests is therefore considered experimental/investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

89240	81535	81536	0564T	0248U

Rationale

This policy was originally based on a 2002 Technology Evaluation Center (TEC) Assessment[10] and a systematic review by Samson et al,[11] which concluded that evidence is insufficient to support use of chemosensitivity and chemoresistance assays for guiding choice of therapy regimen in cancer patients.

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[10,11] 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.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Chemoresistance Assays

Clinical Context and Test Purpose

The purpose of chemoresistance assays is to provide a diagnostic option that is an alternative to or an improvement on existing clinical practice to select treatment regimens in patients with cancer who are initiating chemotherapy.

The question addressed in this evidence review is: Does the use of chemoresistance assays improve the net health outcome in individuals being treated for cancer?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are individuals with cancer who are initiating chemotherapy who are screened with chemoresistance assays.

Interventions

The test being considered is chemoresistance assays.

In vitro chemoresistance 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. Oncologists may sometimes use these assays to select treatment regimens for a patient. Protocol components include (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 results.

There are several methods of chemoresistance assays, differential staining/dye exclusion, radioactive precursors by macromolecules in viable cells, quantifying cell viability using colorimetric assays, and chemoluminescent precursors by macromolecules in viable cells.

Comparators

Comparators of interest include guideline based chemotherapy selection without chemoresistance assay.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy, test validity, and QOL.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

a. The study population represents the population of interest. Eligibility and selection are described.
b. The test is compared with a credible reference standard.
c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
d. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other

measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.

e. Studies should also report reclassification of diagnostic or risk category.

Review of Evidence

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.[10] 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.[12]

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 for several reasons.[11] 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. Without knowing the rules for converting assay findings into treatment choices, it is impossible to determine the effects of assay-guided treatment on health outcomes. 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 et al (1998, 2000),[13,14] Mehta et al (2001),[15] Holloway et al (2002)[16] and Ellis et al (2002).[17]

The 2002 TEC Assessment identified 1 nonrandomized retrospective comparative study using the EDR® assay, by Loizzi et al in 2003.[18] 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 (2003) study, no additional comparative studies of assay-guided therapy versus physician-directed therapy have appeared for chemoresistance assays.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prospective Studies

A study by Tiersten et al (2009) was designed to use the Oncotech EDR assay to examine whether chemotherapy resistance was an independent predictor of progression-free survival

(PFS) in patients with stage III or IV with ovarian cancer.[18] 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 of the 58 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 has not been sufficient to measure OS. 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.[3] 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.[2] Only 41 were eligible for inclusion and were tested with the EVA/PCD™ assay to determine which chemotherapeutic drugs to use. A further 10 patients were excluded (5 due to insufficient cellular yield, 3 for resistance to all drugs tested, and 2 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%) for the assay-directed chemotherapy group, which was significantly greater than the stated historic standard of 30% objective response ($p<0.0001$).

Retrospective Studies

In 2010, Matsuo et al published a study examining the relevance of EDR in epithelial ovarian carcinomas.[20] 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 (e.g., gemcitabine, topotecan, doxorubicin, etoposide, 5-fluorouracil (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 Matsuo et al (2009) evaluated the role of the EDR assay to platinum- and taxane-based therapies for management of advanced epithelial ovarian, fallopian, and peritoneal cancers.[21] 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 PFS and OS compared to the 115 patients (66.5%) who demonstrated IDR or EDR to platinum and/or taxane (5-year OS rates, 41.1% vs. 30.9%, respectively; p=0.014). The 5-year OS 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 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.

A smaller study by Matsuo et al (2010) testing the EDR assay for prediction of uterine carcinosarcoma response to taxane and platinum was also conducted.[22] 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 (1-year PFS rate, 28.6% vs. 100%, respectively; p=0.01) and lower OS (5-year OS rate, 26.9% vs. 57.1%, respectively; 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.

Matsuo et al (2010) also completed a study examining the rates of EDR after cytoreductive therapy and neoadjuvant chemotherapy versus the rates of ERD after postoperative chemotherapy.[23] 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) 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.[24] 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 (median 24-89), 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 (2012) conducted a study to identify primary platinum resistance in epithelial ovarian cancer patients with FIGO stage III-IV disease.[25] 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: 3.2-4.7) compared with the platinum sensitive group with a median PFS of 8.1 months (95% CI: 3.7-12.4). 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.

Section Summary: Clinically Valid
For chemoresistance assays, some retrospective and prospective correlational studies have suggested that these assays may be associated with chemotherapy response. However, prospective studies have not consistently demonstrated that chemoresistance assay results are associated with survival.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of chemosensitivity and chemoresistance assays has not been established, a chain of evidence cannot be constructed.

Section Summary: Chemoresistance Assays
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

Clinical Context and Test Purpose
The purpose of chemosensitivity assays is to provide a diagnostic option that is an alternative to or an improvement on existing clinical practice to select treatment regimens in patients with cancer who are initiating chemotherapy.

The question addressed in this evidence review is: Does the use of chemosensitivity assays improve the net health outcome in individuals being treated for cancer?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with cancer who are initiating chemotherapy.

Interventions
The test being considered is chemosensitivity assays.

Comparators
Comparators of interest include guideline directed chemotherapy selection.

Outcomes
The general outcomes of interest are OS, disease-specific survival, test accuracy, test validity, and QOL.

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.

The TEC Assessment (2002)[10] and systematic review by Samson et al (2004)[11] identified 9 comparative studies, 2 of which were randomized.[26,27,28,29,30,31,32,33,34] 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.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prospective Studies
Kim et al (2010) 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.[35] 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 2 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% 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.

Rutherford et al (2013) reported results from a prospective, non-interventional, 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.[36] Three hundred thirty-five patients were enrolled and treated with 1 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 PFS 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 (2014) 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).[37] 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 (reported as 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, because 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 (2014) 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.[38] 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 (2012) conducted a prospective, non-interventional, multicenter cohort study to assess whether the Microculture Kinetic (MiCK) assay was predictive of outcomes among women with epithelial ovarian cancer.[39] 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. OS stage III or IV disease was longer if patients received a chemotherapy that was considered “best” by the MiCK assay, compared with shorter survival in 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 (HDRA), was predictive of outcomes among women with advanced epithelial ovarian cancer.[40] 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 PFS (35 months vs. 16 months, p=0.025).

Suksawat et al (2019) evaluated the response pattern of individual cholangiocarcinoma (CCA) patients by using an in vitro method, histoculture drug response assay (HDRA), to predict the chemosensitivity of individual patients in a prospective study.[61] Based on the dose response curve, 1000 and 1500 μg/ml of gemcitabine were used as the testing concentrations. For cisplatin, concentrations of 20 and 25 μg/ml were selected for testing and for the combination regimen, 1000 μg/ml of gemcitabine and 20 μg/ml of cisplatin were chosen. The median %IR of each drug was measured as the cut-off to categorize the response pattern into response and non-response groups. In addition, we compared the effectiveness of the chemotherapy regimens between gemcitabine alone and gemcitabine plus cisplatin. The %IR of the combination of gemcitabine and cisplatin was significantly higher than gemcitabine alone. The relationship between the expression level of gemcitabine and cisplatin sensitive factors and the individual response pattern as well as clinicopathological data of CCA patients were analyzed. The results indicated that a low expression of the gemcitabine sensitive factor hENT-1 was significantly associated with the non-response group in vitro (p = 0.002). Moreover, the low expression of hENT-1 was also significantly associated with advanced stages CCA in the patients (p = 0.025). A low expression of MT and ERCC1 was significantly correlated with the response group in the in vitro experiments (p = 0.015 and p = 0.037 for MT and ERCC1, respectively).

Lee et al (2021) retrospectively analyzed the results of HDRAs to determine whether the results could predict platinum sensitivity and prognosis in ovarian cancer.[62] One hundred thirty-nine patients with ovarian cancer were reviewed. HDRAs were conducted for platinum and taxane agents. Platinum resistance and sensitivity occurred in 21 and 118 patients, respectively. To analyze the relationship between the inhibition rates (IRs) of tumor growth caused by the platinum agent and clinical outcomes, Student's t-test and linear regression analysis were used. The average IRs of the platinum and taxane agent were not statistically significant between the platinum-sensitive and - resistant groups. There was no statistical significance for overall survival, progression-free survival, or platinum-free interval. The HDRA is not useful for predicting platinum sensitivity and survival outcomes.

Zhang and Li (2015) evaluated ovarian epithelial cancer cells using an in vitro ATP tumor chemosensitivity assay.[41] 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 NPV 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.

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 week.

In 2016, Tanigawa et al published a retrospective study evaluating the association between in vitro chemosensitivity results and relapse-free survival (RFS) in 206 gastric cancer patients.[42] The collagen gel droplet embedded culture drug sensitivity test is commercially available as a kit in Japan. All patients underwent 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 (non-responders). Median length of follow-up from the time of surgery was 3.2 years. Three-year RFS was significantly higher in the in vitro sensitive (responder) group (82.9%; 95% CI, 74.4% to 91.3%) than in the vitro insensitive (no responder) group (63.4%; 95% CI, 54.7% to 72.1%; p=0.001).

Gallion et al (2006) 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.[43] 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 2 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 9 months for the resistant group, 14 months for the intermediate group, and had not been achieved for the sensitive group.

Herzog et al (2010)[44] included 147 patients from the above study by Gallion et al[43] and reported on 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 (2013) conducted a retrospective analysis to assess the association of pretreatment chemosensitivity to cisplatin with clinical outcomes among 33 women with cervical cancer.[45] 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 the histoculture drug response assays (HDRA) assay in 79 patients with ovarian cancer.[46] 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 3 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 2 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 (2013) conducted a retrospective evaluation of the association between chemosensitivity to anthracyclines, measured by the drug-induced apoptosis MiCK assay, among 109 patients with adult-onset acute myelogenous leukemia.[47] 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 no 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.

Other retrospective studies have evaluated the association between chemosensitivity 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 non-responding patients.[48]

Section Summary: Clinically Valid

For chemosensitivity assays, the evidence includes retrospective and prospective correlational studies. These studies of several different chemosensitivity assays have suggested that patients whose tumors have higher chemosensitivity have better outcomes.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

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.[49] 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).

In 2006, Ugurel et al conducted a nonrandomized, prospective, phase 2 study of 53 evaluable patients with metastatic melanoma.[50] 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 study, Moon et al (2009) retrospectively compared adenosine triphosphate (ATP) assay-based guided chemotherapy with empirical chemotherapy in unresectable non-small-cell lung cancer.[51] All of the patients who received ATP-assay-guided platinum-based doublet chemotherapy as first-line therapy received platinum-based chemotherapy combined with a non-platinum 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 non-platinum 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 2 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 nonrandomized comparative study (n=64), Iwahashi et al (2005) reported on outcomes of chemosensitivity-guided chemotherapy (CSC) compared to standard chemotherapy and no chemotherapy in patients with advanced gastric cancer who had undergone a gastrectomy.[52] 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, randomized trial of chemosensitivity assay-directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer.[53] The primary aim of this randomized trial was to determine response rate and PFS following chemotherapy in patients who had been treated according to an 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 [ITT] analysis, respectively). ITT analysis showed a median PFS 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 OS 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 RCT documented 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 remains an investigational method in this condition.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of chemosensitivity and chemoresistance assays has not been established, a chain of evidence cannot be constructed.

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, which compare outcomes for patients managed with an ATP-based tumor chemosensitivity assay with those managed with standard care, including 1 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 OF EVIDENCE

For individuals who have cancer who are initiating chemotherapy who receive chemoresistant 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 do not consistently demonstrate that chemoresistance assay results are associated with survival. Furthermore, no studies were identified that compared outcomes for patients managed with assay-directed therapy to those managed with physician-directed therapy. Large, randomized, prospective clinical studies comparing clinical outcomes 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 1 randomized controlled trial (RCT), 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 with a chemosensitivity assay to those managed with standard care, including 1 RCT. 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 to better outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03133273[a]	Study of the therapeutic response and survival of patients with metastatic colorectal cancer (stage IV) and treated according to the guidelines of a chemosensitivity test, Oncogramme®	256	Jul 2024
NCT04544969	Detecting chemnosensitivity and predicting treatment efficacy with CTCs in mNPC	50	Dec 2025

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network (NCCN)

Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer
Current NCCN (v.2.2023) guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer state that "Chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3)."[55]

Gastric Cancer
The NCCN (v.2.2023) guidelines for the treatment of gastric cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[56]

Breast Cancer
The NCCN (v.4.2023) guidelines for the treatment of breast cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[57]

Melanoma
The NCCN (v.2.2023) guidelines for the treatment of cutaneous melanoma do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[58]

Non-Small Cell Lung Cancer
The NCCN (v.3.2023) guidelines for the treatment of non-small cell lung cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[59]

Uterine Neoplasm
The NCCN (v.2.2023) guidelines for the treatment of uterine neoplasms do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[60]

American Society of Clinical Oncology

The updated 2011 American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.[61]

Government Regulations

National/Local:

There is no LCD or NCD on chemosensitivity and chemoresistance assays for Michigan.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- CA-125 Testing (retired)
- Detection of Circulating Tumor Cells in the Management of Patients with Cancer
- Genetic Testing to Determine the Prognosis of Breast Cancer Patients
- HER-2/neu and TOP2A Testing for Patients with Breast Cancer (retired)
- Human Epididymis Protein HE4 for Ovarian Cancer
- KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer
- KRAS Mutation Analysis in Non-Small-Cell Lung Cancer (NSCLC)
- Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Cancer
- Oncoprotein Des-gamma-carboxy Prothrombin (DCP) Immunoassay

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62. HAYES Health Technology Brief. ChemoFx Assay (Precision Therapeutics Inc.) for Prediction of Response to Chemotherapy for Ovarian Cancer. Lansdale, PA: HAYES, Inc. August 2016. Archived November 2017.
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/09	9/10/09	8/18/09	Joint medical policy established
11/1/10	8/28/10	8/28/10	Routine maintenance
11/1/11	8/16/11	8/16/11	Routine maintenance
11/1/12	8/21/12	8/21/12	Policy description, rationale and references updated to mirror BCBSA policy.
1/1/14	10/17/13	10/25/13	Routine maintenance
3/1/15	2/17/15	2/27/15	Updated Medicare information to reflect coverage of ChemoFX for Medicare members. Rationale and references updated. Status remains EI for commercial members.
5/1/16	2/16/16	2/16/16	Updated Medicare information with proposed LCD-E/I. Rationale and references updated. Status E/I for commercial/Medicare members.
5/1/17	2/21/17	2/21/17	Routine policy maintenance. No change in policy status.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. Added references 35, 50, 55 and 56. No change in policy status.
1/1/19	10/16/18	10/16/18	Routine policy maintenance. No change in policy status.
1/1/20	10/15/19		Rationale section reformatted. Added code 0564T as E/I. No change in policy status.
1/1/21	10/20/20		Routine policy maintenance. No change in policy status.
1/1/22	10/19/21		Routine policy maintenance, no change in policy status. Added code 0248U as E/I effective 7/1/21.
1/1/23	10/18/22		Routine policy maintenance, no change in policy status.
1/1/24	10/17/23		Updated rationale added reference 61 and 62. No change in policy

			status. Vendor managed: Avalon (ds)

Next Review Date: 4^{th} Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CHEMOSENSITIVITY AND CHEMORESISTANCE ASSAY, IN VITRO

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Not covered

II. Administrative Guidelines:

N/A