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Medical Policy

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Title: In Vitro Chemoresistance and Chemosensitivity Assays

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Populations	Interventions	Comparators	Outcomes
Individuals:	Interventions of interest are: • Chemoresistance assays	Comparators of interest are:	Relevant outcomes include: • Overall survival

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• With cancer who are initiating chemotherapy		• Chemotherapy selection without chemoresistance assay	• Disease-specific survival • Test accuracy • Test validity • Quality of life
Individuals: • With cancer who are initiating chemotherapy	Interventions of interest are: • Chemosensitivity assays	Comparators of interest are: • Chemotherapy selection without chemosensitivity assay	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Quality of life

DESCRIPTION

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. Oncologists may sometimes use these assays to select treatment regimens for a patient. Several assays have been developed that differ concerning the 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.

Objective

The objective of this evidence review is to determine whether the use of chemoresistance and chemosensitivity assays improve the net health outcome in individuals being treated for cancer.

Background

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

METHODS USING DIFFERENTIAL STAINING/DYE EXCLUSION

Differential Staining Cytotoxicity Assay

The Differential Staining Cytotoxicity assay relies on dye exclusion of live cells after mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation.[1,] Cells are then established in culture and treated with the drugs of interest at 3 dose levels: the middle (relevant) dose, which could be achieved in therapy; a 10-fold lower dose than the physiologically relevant dose; and a 10-fold higher dose. Exposure time ranges from 4 to 6 days; then cells are re-stained with fast green dye and counterstained with hematoxylin and eosin. The fast green dye is taken up by dead cells, and hematoxylin and eosin 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 the number of live cells in the treated samples to the number of live cells in the untreated controls.

EVA/PCD Assay

The EVA/PCD assay (Rational Therapeutics) 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 microaggregates are believed to approximate the human tumor microenvironment 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 and fast green dye with glutaraldehyde-fixed avian erythrocytes is added to the cellular suspensions.[2] The samples are then agitated and cytospin-centrifuged and, after air drying, counterstained with hematoxylin and eosin. 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 RADIOACTIVE PRECURSORS BY MACROMOLECULES IN VIABLE CELLS

Tritiated Thymine

Tritiated thymine incorporation measures uptake of tritiated thymidine by DNA of viable cells. Using proteases and DNase to disaggregate the tissue, samples are seeded into single cell suspension cultures on soft agar. They are then treated with the drug(s) of interest for 4 days. After 3 days, tritiated thymidine is added. After 24 hours of additional incubation, cells are lysed, and radioactivity is quantified and compared with a blank control consisting of cells that were treated with sodium azide. Only cells that are viable and proliferating will take up the radioactive thymidine. Therefore, there is an inverse relationship between the update of radioactivity and sensitivity of the cells to the agent(s) of interest.[5]

Extreme Drug Resistance Assay

The Oncotech Extreme Drug Resistance EDRÒ assay (Exiqon Diagnostics; no longer commercially available) is methodologically similar to the thymidine incorporation assay, using metabolic incorporation of tritiated thymidine to measure cell viability; however, single cell suspensions are not required, so the assay is simpler to perform.[6] Tritiated thymidine is added to the cultures of tumor cells, and uptake is quantified after various incubation times. Only live (resistant) cells will

incorporate the compound. Therefore, the level of tritiated thymidine incorporation is directly related to chemoresistance. The interpretation of the results is unique in that resistance to the drugs is evaluated, as opposed to the evaluation of responsiveness. Tumors are considered to be highly resistant when thymidine incorporation is at least 1 standard deviation above reference samples.

METHODS QUANTIFYING CELL VIABILITY USING COLORIMETRIC ASSAY

Histoculture Drug Resistance Assay
The Histoculture Drug Resistance Assay HDRA (AntiCancer) evaluates cell growth after chemotherapy treatment based on a colorimetric assay that relies on mitochondrial dehydrogenases in living cells.[7,]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.

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METHODS USING CHEMOLUMINESCENT PRECURSORS BY MACROMOLECULES IN VIABLE CELLS

Adenosine Triphosphate Bioluminescence Assay

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

ChemoFX Assay

The ChemoFX (Helomics, 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

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

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POLICY

A.   In vitro chemoresistance assays, including, but not limited to, Extreme Drug Resistance assay, are considered **experimental / investigational.**

B.   In vitro chemosensitivity assays, including, but not limited to, the Histoculture Drug Response Assay, a fluorescent cytoprint assay, or the ChemoFX assay, are considered **experimental / investigational.**

RATIONALE
This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 2, 2021.

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

The question addressed in this evidence review is: Does the use of chemoresistance assays improve the net health outcome in individuals with cancer who are initiating chemotherapy?

The following PICO was used to select literature to inform this review.

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

Interventions
The test being considered is chemoresistance assays.

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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 quality of life.

Study Selection Criteria
For the evaluation of clinical validity of chemoresistance assays, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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 TEC Assessment (2002) concluded that chemoresistance assays have the highest clinical relevance in tumors with a 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.[11,]

The bulk of the literature on EDR assays has focused on correlational studies assessing results from predictive in vitro assays and observed outcomes of chemotherapy. However, in these studies, patients did not receive assay-guided chemotherapy regimens. As discussed in the systematic review by Samson et al (2004), correlational studies are inadequate to demonstrate

the clinical utility of chemoresistance assays for several reasons.[12,] First, such studies often aggregate patients with different tumor types, disease characteristics, chemotherapy options, and probabilities of response. This process is problematic because the accuracy of each assay used to predict in vivo response probably varies across different malignancies and patient characteristics. Second, the method by which assay results are translated into treatment decisions is not standardized. Third, it is important to consider not only response but also survival, quality of life, and adverse events. The overall value of assay-guided therapy depends on the net balance of all health outcomes observed after treatment for all patients subjected to testing, regardless of assay results or the accuracy of its predicted response. Examples of some of the earlier published correlation studies of the EDR assay include those by Eltabbakh et al (1998, 2000),[13,14,] Mehta et al (2001),[15,] Holloway et al (2002),[16,] and Ellis et al (2002).[17,] The TEC Assessment (2002) identified a nonrandomized retrospective comparative study by Loizzi et al (2003)[18,] using the EDR assay. While this study of patients with recurrent ovarian cancer found a significantly higher overall response rate, better progression-free survival (PFS), and higher OS among platinum-sensitive patients receiving assay-guided therapy, it was not designed to address potential biases and confounding adequately. 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).

Review of Evidence
This review was informed by a TEC Assessment (2002)[10,] and a systematic review by Samson et al (2004),[12,] which concluded collectively that the evidence was insufficient to support the use of chemoresistance and chemosensitivity assays for guiding the choice of therapy regimen in cancer patients.

Prospective Studies
A study by Tiersten et al (2009) used the Oncotech EDR assay to examine whether chemotherapy resistance was an independent predictor of PFS in patients with stage III or IV ovarian cancer.[19,] Fifty-eight eligible women were prospectively enrolled in this study; however, results from the EDR assay were not used to direct therapy. All women were treated with neoadjuvant chemotherapy and surgical cytoreduction followed by intraperitoneal chemotherapy. Evaluable EDR assay results were available for 22 patients. No difference in PFS was reported among patients who were defined as "resistant" or "nonresistant" to platinum therapy or paclitaxel based on the EDR assay. Follow-up was not sufficient to measure OS. These data do not support the use of the EDR assay in predicting outcomes and guiding patient management.

A review by Nagourney (2006) included 21 noncomparative studies using ex vivo programmed cell death assays.[3,] Selected studies correlated drug susceptibility findings for the ex vivo assay for those with an objective clinical response (complete or partial) and nonresponders (N=659

patients). Nagourney (2006) obtained aggregate positive values by the site of primary cancer: breast (82.9%), colon (80%), non-small-cell lung cancer (66.7%), gynecologic (77%), and small-cell lung cancer (50%). A 2012 study by this same investigator prospectively assessed 98 patients with non-small-cell lung cancer treated between 2003 and 2010.[2,] Only 41 were eligible for inclusion and tested with the ex vivo analysis of programmed cell death assay to determine which chemotherapeutic drugs to use. Another 10 patients were excluded (5 due to insufficient cellular yield, 3 for resistance to all drugs tested, 2 due to physician's choice), yielding only 31 patients who received the assay-recommended treatment. The authors compared results for these 31 patients treated using assay-directed chemotherapy with historical controls (not described) on the outcome of observed objective response rate (complete response and partial response). The objective response rate was 64.5% (95% confidence interval [CI], 46.9% to 78.9%) for the assay-directed chemotherapy group, which was significantly greater than the historic standard rate of 30% objective response (p <.001).

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Retrospective Studies

Matsuo et al (2010) examined the relevance of extreme drug resistance 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 (eg, gemcitabine, topotecan, doxorubicin, etoposide, 5-fluorouracil). Paclitaxel showed the highest resistance rate. Other agents had resistance rates of less than 20%. Only 1 (0.4%) tumor showed complete resistance to all drugs tested, and 25% of tumors showed no resistance to any of the drugs. There was no statistical correlation between assay results and response to initial chemotherapy. Investigators acknowledged that the study, due to its retrospective and noncomparative design, was not sufficient to validate the use of this assay in managing therapy. Potential confounding factors, described by investigators, included tumor heterogeneity and variations in resistance between primary tumor and metastases.

In a smaller study (N=51) by Matsuo et al (2010) that evaluated the predictive value of the EDR assay for uterine carcinosarcoma response to taxane and platinum, 31 (60.8%) patients received postoperative chemotherapy with at least a single agent and 17 (33.3%) received combination chemotherapy with platinum and taxane modalities.[21,] The overall response rate for the 17 combination chemotherapy cases was 70.6%. The presence of extreme drug resistance to platinum or taxane showed a significantly lower 1-year PFS rate (28.6% vs 100%, respectively; p =.01) and lower 5-year OS rate (26.9% vs 57.1%, respectively; p =.033). These data would indicate that the use of an in vitro drug resistance assay might be predictive of response to chemotherapy response and survival outcome in advanced ovarian and uterine carcinosarcoma.

Matsuo et al (2010) also compared the rates of extreme drug resistance after cytoreductive therapy and neoadjuvant chemotherapy with the rates of extreme drug resistance after postoperative chemotherapy.[22,] 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.

Another study by Matsuo et al (2009) evaluated the potential of the EDR assay to guide the selection of platinum- and taxane-based therapies for the management of patients with advanced epithelial ovarian, fallopian, and peritoneal cancers.[23,] From the Oncotech database, 173 cases were identified. For all cases, tissue was collected at the time of cytoreductive therapy. The EDR assay was used to assess all samples, and tumors were classified as having low drug resistance, intermediate drug resistance, or extreme drug resistance. The 58 (33.5%) patients whose tumors had low drug resistance to both platinum and taxane showed statistically improved 5-year PFS and OS compared with the 115 (66.5%) patients who demonstrated intermediate or extreme drug resistance to platinum and/or taxane (5-year OS rates, 41.1% vs 30.9%, respectively; p =.014). The 5-year OS rate in the 28 (16.2%) cases who had optimal cytoreduction with low drug resistance to both platinum and taxane (54.1%) was significantly better than that for the 62

(35.8%) cases who were suboptimally cytoreduced with intermediate or extreme drug resistance to platinum and/or taxane (20.4%; p <.001). Although the EDR assay was predictive for survival, assay results did not indicate a response to therapy with taxane or cisplatin. The investigators concluded that the EDR assay might be an independent predictor of PFS and OS; however, a prospective, randomized trial would be required to further assess its clinical utility in predicting response to taxane or platinum therapies.

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

Hetland et al (2012) studied primary platinum resistance in epithelial ovarian cancer patients with Federation of Gynecologists and Obstetricians stage III or IV disease.[25,] Eighty-five biopsies from 58 patients were included. Resistance was assessed with a modified drug response assay including adenosine triphosphate (ATP)-based tumor chemosensitivity and EDR assay. Samples were tested for response to platinum, paclitaxel, and a combination of the drugs. Results from the assay were combined, and tumors were classified using a resistance index, which summarized the percentage of tumor growth inhibition for each drug concentration tested. All patients received a primary chemotherapy treatment of carboplatin, paclitaxel, or a combination of the 2 drugs. Platinum resistance, as defined by the risk index, was associated with significantly poorer PFS (median value, 3.9 months; 95% CI, 3.2 to 4.7 months) than platinum sensitivity (median PFS, 8.1 months; 95% CI, 3.7 to 12.4 months). Patients who had a partial response, stable disease or a progressive disease were more resistant to platinum-based chemotherapy on the risk index score than those with a complete response (p=0.02). In a subgroup analysis of metastatic tumors, platinum resistance was not associated with PFS or clinical response. Response to paclitaxel or carboplatin plus paclitaxel was not associated with PFS or clinical response. In vitro response was not associated with OS in any group.

Section Summary: Clinically Valid
A variety of studies have reported a correlation between in vitro prediction or response and clinical response. While these studies may have internal validity, they cannot answer whether patients given assay-guided therapy or empirical therapy have different outcomes. To determine whether assay-guided treatment results in overall different outcomes than empirical treatment, it

is important to take into account response rates, survival, adverse events, and quality of life. These effects may be assessed indirectly (eg, using decision analysis) or directly with comparative trials. Both the 2002 TEC Assessment and the 2004 systematic review[10,12,] recommended validating chemotherapy resistance and sensitivity assays with direct evidence gathered from prospective trials comparing patients treated empirically with patients treated with assay-directed therapy. In this way, not only can response rates and survival be taken into account, but also adverse events (eg, from the toxic effects of an ineffective drug or delay or loss of benefits of an effective drug) and quality of life.

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 chemoresistance assays has not been established, a chain of evidence cannot be constructed.

Section Summary: Chemoresistance Assays
Some retrospective and prospective studies have suggested that chemoresistance assays, particularly the EDR assay, may be associated with chemotherapy response. However, prospective studies have not consistently demonstrated that chemoresistance assay results are associated with survival. Furthermore, no comparative studies were identified that evaluated outcomes among patients managed with assay-directed therapy and those managed with physician-directed therapy. Large, randomized, prospective clinical studies comparing outcomes, including OS, disease-specific survival, quality of life, and adverse events, between assay-directed therapy and physician-directed therapy are needed.

CHEMOSENSITIVITY ASSAYS
Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does the use of chemosensitivity assays improve the net health outcome in individuals with cancer who are initiating chemotherapy?

The following PICO was used to select literature to inform this review.

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

Interventions
The test being considered is chemosensitivity assays.

Comparators
Comparators of interest include guideline directed chemotherapy selection without chemosensitivity assays.

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

Study Selection Criteria
For the evaluation of clinical validity of the chemosensitivity assay test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Chemosensitivity assays are designed to select the most appropriate chemotherapy regimens for a given tumor type, and would therefore ideally be associated with high positive predictive values for clinical response. The critical type of evidence needed to establish the effectiveness of chemosensitivity assays would come from comparative studies of assay-guided therapy versus physician-directed therapy.

Review of Evidence
This review was informed by a TEC Assessment (2002)[10,] and a systematic review by Samson et al (2004),[12,] which concluded collectively that the evidence was insufficient to support the use of chemoresistance and chemosensitivity assays for guiding the choice of therapy regimen in cancer patients.

The TEC Assessment (2002)[10,] and systematic review by Samson et al (2004)[12,] 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 on the results of a prospective, multicenter clinical trial designed to define the accuracy of the ATP-based chemotherapy response assay in gastric cancer patients receiving paclitaxel and cisplatin chemotherapy, by comparing clinical response and the ATP

assay results.[35,] The primary study outcome was the accuracy of the ATP assay results, and the secondary outcome was finding the best method of defining in vitro chemosensitivity. Forty-eight patients with chemotherapy-naive, 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 the World Health Organization criteria using a computed tomography scan after every 2 cycles of chemotherapy. Laboratory technicians and physicians were blinded to the assay or clinical results. Thirty-six patients were evaluable for both in vitro and in vivo responses. Using a chemosensitivity index method, the specificity of the ATP assay was 95.7% (95% CI, 77.2% to 99.9%), sensitivity was 46.2% (95% CI, 19.2% to 74.9%), positive predictive value was 85.7% (95% CI, 42.1% to 99.6%), and NPV was 75.9% (95% CI, 55.1% to 89.3%). Median PFS was 4.2 months (95% CI, 3.4 to 5.0 months) and median OS was 11.8 months (95% CI, 9.7 to 13.8 months). The in vitro chemosensitive group showed a higher response rate (85.7%) than the chemoresistant group (24.1%; p =.005). 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 on results from a prospective, noninterventional, multicenter cohort study designed to assess whether the ChemoFX assay was predictive of outcomes among women (N=335) with histologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.[36,] Patients were treated with 1 of 15 study protocols; treating physicians were blinded to the ChemoFX assay result. Two hundred sixty-two (78.2% of total) patients had both available clinical follow-up data and a ChemoFX result. Cancer cells were classified based on the ChemoFX result as sensitive, intermediate, or resistant to each of several chemotherapeutic agents. Patients treated with an assay-sensitive regimen had a median PFS of 8.8 months compared with 5.9 months for those with assay-intermediate or -resistant regimens (hazard ratio [HR], 0.67; p =.009). Mean OS was 37.5 months for patients treated with an assay-sensitive regimen and 23.9 months for those with assay-intermediate or -resistant regimens (HR, 0.67; p =.010).

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

Krivak et al (2014) reported on results of a subsequent prospective, observational, multicenter study to determine whether sensitivity to carboplatin and/or paclitaxel was associated with disease progression among patients with primary epithelial ovarian cancer following initial treatment with a platinum plus taxane regimen.[38,] A total of 462 patients were enrolled, with 276 evaluable for analysis. Assay results for carboplatin and paclitaxel were available for 231 and 226 patients, respectively, with 44 (19.1%) patients identified as carboplatin-resistant and 49 (21.7%) identified as paclitaxel-resistant. Carboplatin-resistant patients were at a higher risk of disease progression than nonresistant patients (HR, 1.87; 95% CI, 1.29 to 2.70; p <.001). In a similar study design, Salom et al (2012) conducted a prospective, noninterventional, multicenter cohort study to assess whether the Microculture Kinetic (MiCK) assay (now called CorrectChemo) was predictive of outcomes among women with epithelial ovarian cancer.[39,] Data from 150 women with any stage of cancer and specimens suitable for MiCK assay were included. Chemosensitivity was expressed as kinetic units following each dose of the drug in the MiCK assay and reported as mean, minimum, and maximum. For each patient, the "best" chemotherapy was defined as any single drug or combination of drugs in the patient's MiCK assay that had the highest kinetic units. Patients' regimens were at the discretion of treating physicians, who were blinded to the MiCK assay results. Overall survival for stage III or IV disease was longer if patients received chemotherapy considered "best" by the MiCK assay, compared with shorter OS for patients who received chemotherapy that was not the best (HR, 0.23; p <.01).

Jung et al (2013) conducted a single-center prospective study to determine whether sensitivity to paclitaxel and carboplatin, determined by using the Histoculture Drug Resistance Assay, was predictive of outcomes among 104 women with advanced epithelial ovarian cancer.[40,] All patients had undergone initial surgery and were treated with paclitaxel and carboplatin therapy. Tumor cell sensitivity to the chemotherapy agents was classified as sensitive, intermediate, or resistant to paclitaxel, carboplatin, or both, based on the Histoculture Drug Resistance Assay. Patients whose tumors were sensitive to both drugs had a lower recurrence rate than those with resistance to both drugs (29.2% vs 69.8%, p =.02) and had a longer PFS (35 months vs 16 months; p =.025).

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

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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.

Tanigawa et al (2016) published a retrospective study evaluating the association between in vitro chemosensitivity results and relapse-free survival 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 (nonresponders). The median length of follow-up from the time of surgery was 3.2 years. Three-year relapse-free survival was significantly higher in the in vitro sensitive (responder) group (82.9%; 95% CI, 74.4% to 91.3%) than in the vitro insensitive (nonresponder) group (63.4%; 95% CI, 54.7% to 72.1%; p =.001).

Gallion et al (2006) retrospectively evaluated the association between ChemoFX test results and the treatment response for 256 patients with ovarian or peritoneal cancer treated with at least 1 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 or calculable. For the subset of 135, in a multivariable analysis, ChemoFX was an independent significant predictor (p =.006) of PFS along with 2 other clinical variables. The HR was 2.9 (95% CI, 1.4 to 6.30) for resistant versus sensitive and 1.7 (95% CI, 1.2 to 2.5) for resistant versus intermediate. The median PFS was 9 months for the resistant group, 14 months for the intermediate group, and had not been achieved at reporting for the sensitive group.

Herzog et al (2010)[44,] included 147 patients from the Gallion study[43,] and reported on 192 women with advanced stage primary ovarian cancer, 175 of whom had tumors tested for in vitro chemosensitivity to platinum therapy using ChemoFX. Tumors were classified as responsive, intermediately responsive, or nonresponsive to chemotherapy. Seventy-eight percent were categorized as responsive or intermediately responsive, and 22% were nonresponsive. Median OS was 72.5 months for patients with tumors categorized as responsive, 48.6 months for intermediately responsive, and 28.2 months for nonresponsive (HR, 0.70; 95% CI, 0.50 to 0.97; p =.03). The authors concluded that the results of chemosensitivity testing with a drug response marker for therapy were predictive of OS in patients with primary ovarian cancer.

In a smaller study, Grigsby et al (2013) retrospectively analyzed the association between pretreatment chemosensitivity to cisplatin and clinical outcomes in 33 women with cervical cancer.[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 =.036).

Lee et al (2012) conducted a retrospective study of Histoculture Drug Resistance 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 with cisplatin (34.7%), the traditional drug used to treat epithelial ovarian cancer. Outcomes for a subset of 37 patients with Federation of Gynecologists and Obstetricians stages II through IV epithelial ovarian serous adenocarcinoma who had been treated with at least 3 cycles of carboplatin chemotherapy were assessed with carboplatin-sensitive and -resistant patients. Multiple comparisons and regression analyses established a 40% inhibition rate cutoff value in response to 50 mg/mL carboplatin to determine sensitivity or resistance. This selected cutoff had a disease-free survival of 23.2 months (95% CI, 6.3 to 55.3 months) and 13.8 months (95% CI, 4.9 to 35.6 months) in the carboplatin-sensitive and carboplatin-resistant groups, respectively (p <.05). Mean OS between groups did not differ significantly (carboplatin-sensitive patients, 60.4 months vs carboplatin-resistant patients, 37.3 months; p =.621).

Strickland et al (2013) retrospectively evaluated the association between chemosensitivity and anthracyclines, measured by the drug-induced apoptosis MiCK assay, among 109 patients with adult-onset acute myelogenous leukemia.[47,] Patients were treated with a "7 plus 3" chemotherapy regimen. Chemosensitivity was expressed as maximal kinetic units following each dose of the drug in the MiCK assay. Receiver operator characteristic curve analysis and logistic regression were used to determine the optimal cutoff for chemosensitivity response to discriminate between chemoresponder and nonresponder. Patients determined to be chemoresponders to idarubicin were more likely to have a complete response to chemotherapy (72%) than those who were nonresponders (p =.01). Data for the patient cohort were collected over 14 years, from 1996 to 2010, which would limit the generalizability of the results to current chemotherapy regimens.

Other retrospective studies have evaluated chemosensitivity results as measured by other assay types. Von Heideman et al (2014) evaluated the semi-automated fluorometric microculture cytotoxicity assay in 112 patients (125 samples) with ovarian cancer and concluded that samples from patients with clinical response were more sensitive to most drugs than samples from nonresponding patients.[48,]

Section Summary: Clinically Valid

A variety of studies have reported a correlation between in vitro prediction or response and clinical response. While these studies may have internal validity, they cannot answer whether patients given assay-guided therapy or empirical therapy have different outcomes. To determine whether assay-guided treatment results in overall different outcomes than empirical treatment, it is important to take into account response rates, survival, adverse events, and quality of life. These effects may be assessed indirectly (eg, using decision analysis) or directly with comparative trials. Both the 2002 TEC Assessment and the 2004 systematic review[10,12,] recommended validating chemotherapy resistance and sensitivity assays with direct evidence gathered from prospective trials comparing patients treated empirically with patients treated with

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assay-directed therapy. In this way, not only can response rates and survival be taken into account, but also adverse events (eg, from the toxic effects of an ineffective drug or delay or loss of benefits of an effective drug) and quality of life.

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 patients treated with physician-chosen therapy.

Bosserman et al (2015) 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 choose whether to 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 =.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). Overall survival did not differ significantly between patients whose physicians used the assay (16.8 months) and patients whose physicians did not (13.1 months).

Ugurel et al (2006) conducted a nonrandomized, prospective phase 2 trial, 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.

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In a case-control retrospective trial, Moon et al (2009) retrospectively compared ATP assay-based guided chemotherapy with empirical chemotherapy in unresectable non-small-cell lung cancer.[51,] All patients who received ATP assay-guided platinum-based doublet chemotherapy as first-line therapy received platinum-based chemotherapy combined with a nonplatinum drug, regardless of their in vitro platinum sensitivity; 14 patients had platinum-sensitive disease, and 13 were platinum-resistant. Ninety-three matched controls (matched for performance status, stage, and chemotherapy regimen) were selected from a retrospective review of a database. In the empirical group, a nonplatinum drug was chosen, depending on physicians' discretion, along with a platinum agent determined by renal function and performance status. The primary endpoint was clinical response rate, assessed every 2 cycles of chemotherapy using the Response Evaluation Criteria in Solid Tumors criteria. The secondary endpoints were PFS and OS. Response and survival rates in both groups did not differ statistically. By ATP assay, the platinum-sensitive subgroup (71%) showed a higher response rate than the empirical group (38%; p =.02), but PFS and OS differences between groups were not statistically significant.

In a nonrandomized prospective study (N=64), Iwahashi et al (2005) reported on outcomes of chemosensitivity-guided chemotherapy compared with standard chemotherapy and no chemotherapy in patients with advanced gastric cancer who had undergone a gastrectomy.[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 RCT of chemosensitivity assay-directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer.[53,] The primary aim of this RCT was to determine response and PFS rates following chemotherapy in patients treated based on an ATP-based tumor chemosensitivity assay or physician-choice. A total of 180 patients were randomized to assay-directed therapy (n=94) or to physician-choice chemotherapy (n=86). Median follow-up at analysis was 18 months; the response was assessable in 147 (82%) patients: 31.5% achieved a partial or complete response in the physician-choice group compared with 40.5% in the assay-directed group (26% vs 31% by intention-to-treat analysis, respectively). Intention-to-treat analysis showed a median PFS of 93 days in the physician-choice group and 104 days in the assay-directed group (HR, 0.8; p =.14). No difference was reported in OS between groups, although 12 (41%) of 39 patients who crossed over from the physician-choice arm obtained a response. Increased use of combination therapy was seen in the physician-choice arm during the trial as a result of the observed effects of assay-directed therapy in patients. The authors concluded that this small RCT suggested a trend toward improved response and PFS for assay-directed treatment and that chemosensitivity testing might provide useful information in some patients with ovarian cancer. They also noted that the ATP-based tumor chemosensitivity assay would remain an investigational method in this condition.

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

Summary of Evidence

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

For individuals with cancer who are initiating chemotherapy and receive chemosensitivity assays, the evidence includes a randomized controlled trial, nonrandomized studies, and correlational observational studies. Relevant outcomes are OS, 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, including a randomized controlled trial, comparing outcomes for patients managed using a chemosensitivity assay with those managed using standard care. Although some improvements in tumor response were noted in the randomized trial, there were no differences in survival outcomes. One small nonrandomized study reported improved OS 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

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to determine whether the clinical use of in vitro chemosensitivity testing leads to improvements in OS are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

NATIONAL COMPREHENSIVE CANCER NETWORK
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer
Current National Comprehensive Cancer Network (NCCN) (v.1. 2021) 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)."

Gastric Cancer
The NCCN (v.2. 2021) guidelines for the treatment of gastric cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[54,]

Breast Cancer
The NCCN (v.4. 2021) guidelines for the treatment of breast cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[55,]

Melanoma
The NCCN (v. 2.2021) guidelines for the treatment of cutaneous melanoma do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[56,]

Non-Small Cell Lung Cancer
The NCCN (v. 4.2021) 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.[57,]

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Uterine Neoplasms
The NCCN (v. 2.2021) guidelines for the treatment of uterine neoplasms do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.[58,]

American Society of Clinical Oncology
The updated American Society of Clinical Oncology (2011) clinical guidelines on the use of chemotherapy sensitivity and resistance assays did not recommend the use of chemotherapy sensitivity and resistance assays unless in a clinical trial setting.[59,]

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

Ongoing and Unpublished Clinical Trials
The ongoing 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 2022

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS
0564T   Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported

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	based on percent of cytotoxicity observed, a minimum of 14 drugs or drug combinations
81535	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
81536	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 each additional single drug or drug combination (List separately in addition to code for primary procedure)
87230	Toxin or antitoxin assay, tissue culture (e.g., Clostridium difficile toxin)
88104	Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation
88305	Level IV - Surgical pathology, gross and microscopic examination
88313	Special stain including interpretation and report; Group II, all other (e.g., iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry
88358	Morphometric analysis; tumor (e.g., DNA ploidy)
89050	Cell count, miscellaneous body fluids (e.g., cerebrospinal fluid, joint fluid), except blood

DIAGNOSIS
Experimental / investigational for all diagnoses related to this policy.

REVISIONS	
09-20-2011	Policy added to the bcbsks.com web site.
06-29-2012	Description section updated.
	In Coding section: Coding nomenclature updated
	Rationale section added.
	References section updated.
09-25-2013	Description section updated
	Rationale section updated
	References updated
12-14-2015	Published 12-14-2015. Effective 12-14-2015.
	Description section updated
	In Policy section: ▪ In Item A removed "or" and added "the ChemoFx assay, or the CorrectChemo assay," to read "In vitro chemosensitivity assays, including, but not limited to, the Histoculture Drug Response Assay, a fluorescent cytoprint assay, the ChemoFx assay, or the CorrectChemo assay, are considered experimental / investigational."
	Rationale section updated
	In Coding section: ▪ Added CPT codes: 81535, 81536 (Effective January 1, 2016)

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REVISIONS

	▪ Updated Coding notations
	References updated
01-18-2017	Description section updated
	Rationale section updated
	In Coding Section: ▪ Updated Coding notations.
	References updated
11-15-2017	Description section updated
	Rationale section updated
	References updated
09-12-2018	Description section updated
	In Policy section: ▪ In Item B removed "or the CorrectChemo assay" as this test is no longer commercially available.
	Rationale section updated
	References updated
08-28-2019	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notation updated.
	References updated
05-23-2021	Description section updated
	Rationale section updated
	In Coding section: ▪ Added Code 0564T and removed code 89240
	References updated
09-10-2021	Rationale section updated
	References updated
	Medical Policy archived

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