Medical Coverage Policy

Effective Date.....5/15/2025
Next Review Date.....5/15/2026
Coverage Policy Number..... 0203

Tumor In Vitro Chemosensitivity and Chemoresistance Assays

Table of Contents

Related Coverage Resources

Genetics
Laboratory Management Clinical Guidelines
Laboratory Testing Services

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses tumor in vitro chemosensitivity and chemoresistance assays.

Chemosensitivity and chemoresistance assays are in vitro laboratory tests intended to assist in selecting optimal chemotherapies in an individual with cancer, based on tumor cell response.

Coverage Policy

Tumor in vitro chemosensitivity or chemoresistance assays are considered experimental, investigational or unproven.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

The goals of chemotherapy treatment are to utilize the most effective agents for killing tumors or cancer-cells, while avoiding patient toxicity. Various factors are taken into consideration when choosing a chemotherapy regimen including the type of cancer, stage of cancer, other medical conditions of the individual, concomitant drug therapies, and previous chemotherapy. Clinical assessment, imaging techniques, and surgical staging are considered the standards of care for identifying response to therapy.

In vitro studies are conducted using components of an organism that have been isolated from their biological surroundings and studied in artificial culture media or solutions. In vitro chemotherapy sensitivity and resistance assays (CSRAs) have been proposed as methods for determining response and for customizing cancer therapies for individuals. CSRAs are in vitro laboratory analyses of sample cells taken from a primary or metastatic tumor (before or after treatment with chemotherapy) to provide predictive information regarding a tumor's particular chemotherapy sensitivity or resistance (Burstein, 2011). The underlying hypothesis for in vitro assays is that the drug response profile for an individual will undoubtedly differ based on their intrinsic genetic diversity and the development of tumor subclones (Harry, 2009). By determining

the cellular response to these agents, it is hypothesized that individualized treatment protocols may be planned.

In vitro testing has not yet gained widespread acceptance, and there is continued debate concerning its optimal clinical applicability (Harry, 2009). Published guidelines of the National Comprehensive Cancer Network (NCCN®) and the American Society of Clinical Oncology (ASCO) do not endorse the clinical usefulness of in vitro chemosensitivity or chemoresistance assays.

Chemosensitivity Assays: The goal of in vitro chemosensitivity assays is to assist with the selection of chemotherapy drugs for the treatment of cancer in individuals based on the response of each patient's tumor cells to a specific chemotherapeutic agent(s). Tumor cells are obtained from the individual with cancer, cultured in the laboratory, and exposed to a specific drug or battery of drugs over a period of time. If these assays demonstrate excellent predictability they could potentially be helpful in treating patients with curable diseases and allow for the identification of the rare patient with primary resistant disease.

Chemoresistance Assays: In vitro chemoresistance assays are used to identify or deselect those chemotherapy drugs that are non-responsive to a specific tumor. During the assay, tumor cells are cultured and exposed to concentrations of selected chemotherapeutic agents over a prolonged period of time. Tumors are reported as having high, intermediate or low drug resistance, with the assumption being that drugs with low resistance may be effective in vivo (i.e., within the body), while high-resistance drugs may be less effective. According to Harry et al. (2009) the accuracy of in vitro testing in identifying clinical drug resistance is 90%, with a 70% positive predictive value.

Limitations of Chemosensitivity and Resistance Assays (CSRAs): The use of in vitro assays to detect chemosensitivity or resistance has not yet been adapted into routine clinical practice. The ability of these tests to identify active and inactive chemotherapy agents in the laboratory setting does not necessarily translate into an accurate and clinically useful prediction of patient response to therapy and patient survival (Harry, 2009). The precise pathway of apoptosis (i.e., cell death) is difficult to determine and is dependent on several factors, including tumor cell type and volume, the drug combinations being used and the doses that are being prescribed. Some tumor cell components provide protection of the cancer cell against chemolytic agents and act as transporters moving the drugs away from the tumor cells.

A major limitation of CSRAs stems from the need to use in vitro cell culture. In vitro sensitivity or resistance to an agent does not ensure in vivo (i.e., testing on a living organism) response because of a variety of host factors, including drug concentration within the body, vascularity to the tumor or the presence of pharmacologic sanctuaries, such as the blood-brain barrier, and detoxification of the drug within the body. Additionally, tumor growth in vitro may not mirror tumor growth in vivo, nor can it be established that the biopsy tissue used in the assays is truly representative of the entire tumor. The genetic variations suited to survival in culture may yield an altered phenotype. Additionally, the immune system is known to interact with, and in some instances alter, the growth of tumor (Ferriss, 2010). Other limitations of in vitro assays include the need for complex labor intensive laboratory work, the generally low yield of assays and the prolonged time required for results which limits the ability to allow for early prediction of therapy response (Harry, 2009).

Data are limited regarding the clinical usefulness of cellular drug sensitivity and resistance assays. According to Schrag et al. (2004), the chemotherapy combination that often looks most promising on the basis of the CSRA is the same one that would have been chosen in the absence of assay results. If the assay rarely alters the recommended treatment strategy, and results consistently serve to validate the use of the same therapies that would be selected on the basis of the clinical trial literature, utility is limited.

At present, published studies in the peer-reviewed scientific literature are limited by uncontrolled study design, small patient numbers, and the availability of newer chemotherapeutic agents since the advent of these studies. There are limited prospective randomized studies comparing response rates or disease-free survival of patients receiving assay-assisted therapy to those receiving empirical therapy (i.e., choice of treatment based on current evidence of patient outcome) (Harry, 2009). The overall effect on health outcomes is unknown.

Testing Methods: While varying techniques may be used during processing, each test involves the same basic steps of tumor sampling and cell isolation, establishment of cell culture, incubation of cells with chemolytic agents, analysis of results and verification of positive and negative controls (Ferriss, 2010). Several tests are briefly described below.

Chemosensitivity and resistance testing methods include (this list may not be all-inclusive):

- extreme drug resistance assays
- 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H tetrazolium bromide (MTS/MTT) assay
- drug response assay (e.g., ChemoFX Assay®, Helomics™, Inc., formerly Precision Therapeutics, Inc., Pittsburgh, PA)
- microculture kinetic assays of apoptosis (e.g., CorrectChemo® also known as the MiCK®, Perian™ Biosciences, formerly Diatech Oncology, Nashville, TN)
- flow cytometric chemosensitivity assays (FCCA)
- adenosine triphosphate (ATP) assays
- histoculture drug resistance assays (HDRA®, Anticancer, Inc., San Diego, CA)
- fluorescence (cytoprint) assays
- differential staining cytotoxicity assays
- human tumor stem cell assays (HTCA)
- human tumor cloning assays

Newer techniques include ex vivo 3D cell culture platforms (Kiyatec, Inc.) and reverse phase protein array (RPPA) (Theralink® Technologies). Ex vivo 3D cell culture platforms use live cancer cells from surgical or biopsy specimens to create a patient-specific in vivo-like tumor that is used to predict response to approved and investigational cancer drugs. This technique uses in vitro assessment of drug-on-tumor cell interaction prior to in vivo therapy administration. RPPA measures the abundance and activation of cell surface receptor proteins and their downstream signaling pathways. These biomolecules serve as the drug targets for most FDA-approved and investigational therapies for cancer. RPPA is proposed to prevent the patient from being exposed to cytotoxic treatments that might not achieve clinically benefits, while guiding physicians to prescribe treatments that are likely to be therapeutic.

Literature Review: Randomized controlled clinical trial data are lacking regarding improved survival outcomes in patients for whom chemotherapy is directed by in vitro chemosensitivity or chemoresistance assay results. Although a number of uncontrolled clinical trials have been conducted, standards have not been established for the use of tumor in vitro chemosensitivity or chemoresistance assays to direct clinical practice. To date the majority of studies have been small in participant numbers, correlational in design, and do not evaluate outcomes of individuals receiving assay-directed therapy compared with those who receive physician/empiric-driven therapy.

While a trend toward increased response rates and survival has been reported in several studies for various assays, no statistically significant differences have been demonstrated in other studies, including results of a randomized controlled trial published by Cree et al. (2007). Large comparative studies are needed to demonstrate that assay-guided treatment results in improved

health outcomes compared with outcomes achieved with physician-directed therapy. At this time there is insufficient evidence to demonstrate the clinical correlation between the use of these tests and improved patient health outcomes. Further, professional society/organizational consensus support in the form of published guidelines is lacking. Although an active focus of research, the clinical utility of in vitro chemoresistance and chemosensitivity assays has not yet been established.

A systematic review by Samson et al. (2004) evaluated the efficacy of therapy that is guided by chemotherapy sensitivity and resistance assays (CSRAs) compared to empiric chemotherapy, with an emphasis on patient survival outcomes. Of the eleven studies included in this review, two studies randomly assigned patients to either assay-guided treatment or empiric treatment. Although higher response rates were seen in patients with assay-guided treatment compared to patients treated with empiric therapy, outcomes were not statistically significant. These studies were limited by study design, lack of patient survival documentation and reporting of adverse event data.

The American Society of Clinical Oncologists (ASCO) published a systematic review and analysis of the medical literature (Burstein, et al., 2011) regarding the effectiveness of chemosensitivity and chemoresistance assays. ASCO notes that published literature was included or excluded based on the following criteria: outcome comparisons (prospective or retrospective) for patients whose chemotherapy was chosen empirically (based on clinical trial literature) as opposed to selection based on results of CSRAs; CSRA performance on viable patient tumor tissue as opposed to other forms of diagnostic testing performed on nonviable tumor tissue; a study sample size of ≥ 20 patients per arm; and primary end points of cancer events or survival including overall survival (OS) and/or response to therapy, disease-free survival, progression-free survival, local tumor control, and/or treatment toxicity. Four publications were selected for inclusion in the review. Additionally, ASCO reviewed data from several published studies involving use of the ChemoFX assay. Limitations to the studies included lack of blinding, lack of comparison groups and selection of chemotherapy at the discretion of the treating physician. Review of the literature did not identify CSRAs for which the evidence base was sufficient to support use in oncology practice. ASCO notes the use of CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting.

Extreme Drug Resistance (EDR) Assay: In this assay, human tumor cells are cultured and exposed to high concentration of drugs for a prolonged period. Tumor cells that survive this overwhelming exposure are considered to demonstrate 'extreme drug resistance'.

Matsuo et al. (2010) retrospectively evaluated the role of in vitro EDR assay to predict the response to platinum and taxane combination chemotherapy in women with advanced ovarian and uterine carcinosarcoma. Fifty-one samples were available in which EDR results were known; of these 17 women received combination chemotherapy. Clinical response to chemotherapy in the presence of EDR to at least one of the two drugs (EDR-PT) was significantly lower than non-EDR-PT (37.5% versus 100%, respectively, p=0.009). Sensitivity, specificity, and positive and negative predictive values for clinical response in non-EDR-PT were 75%, 100%, 100%, and 62.5%, respectively. EDR-PT showed a significantly lower one-year progression-free survival (28.6% versus 100%, respectively), and five-year overall survival (26.9% versus 57.1%, respectively).

In a nonrandomized comparison Joo et al. (2009) evaluated 78 patients with epithelial ovarian cancer, tubal cancer or primary peritoneal carcinoma, with 39 patients in the EDRA group and 39 patients in the physician's choice/empiric therapy group. There was no significant difference in overall response rate between EDRA group and the control group 84.5% vs. 71.8%, respectively, p=0.107). However, 93.8% of patients in EDRA group did not show EDR to at least one drug and

its response rate was significantly higher than that of the control group (93.3% vs. 71.8%, p=0.023).

Karam et al. (2009) conducted a retrospective review of EDR assay and clinical outcomes from 377 individuals with epithelial ovarian cancer who had an assay performed at the time of their primary or subsequent cytoreductive surgeries. EDR assay failed to independently predict or alter outcomes in individuals treated with current standards of primary cytoreductive surgery followed by platinum and taxane combination chemotherapy.

Cloven et al. (2004) reported the retrospective serial results of 5195 epithelial ovarian cancers that were studied to determine whether any relationship existed between histological subtypes and chemoresistance. The EDR assay was used to determine the responsiveness of each subset during exposure to standard chemotherapeutic agents. Although there were significant differences in the frequencies of response and biomarker expression among the histologic subtypes, patient survival benefits with in vitro selected treatment remain unproven.

Loizzi et al. (2003) reported the results of a retrospective study of 50 women with recurrent ovarian carcinoma who were treated with a chemotherapy regimen based on EDR assay guidance compared with results of a control group (n=50) who were treated empirically. In the platinum-sensitive group, individuals with extreme drug resistance-directed therapy had an improved response rate compared with those treated empirically (65% versus 35%, p=0.02). Overall and progression-free survival was also improved in the EDR assay group compared with the control group (p=0.005 overall; p=0.02 progression-free, respectively). Outcomes were not improved for the patients who underwent assay-guided therapy in the platinum-resistant group. In multivariate analysis, platinum-sensitive disease, EDR-guided therapy and early stage of disease were independent predictors for improved survival.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

3-(4, 5-Dimethyl-2-Thiazolyl)-2, 5-Diphenyl-2H Tetrazolium Bromide (MTS/MTT) assay: In this chemosensitivity assay, single tumor cell suspensions are exposed to MTT. If cells are metabolically active, blue crystals are formed.

Wu et al. (2008) reported no significantly different outcomes (p=0.57) between 353 consecutive patients with gastric cancer treated with 3-(4, 5-Dimethyl-2-Thiazolyl)-2, 5-Diphenyl-2H Tetrazolium Bromide (MTT)-directed chemotherapy (n=157) or physician's empirical chemotherapy (n=196). The overall 5-year survival rates of the MTT-sensitive group (MSG) and control group (CG) were 47.5% and 45.1%, respectively. This retrospective study suggests that the clinical benefit of the MTT chemosensitivity assay is limited.

To evaluate the predictive value of an in vitro MTT assay Jun et al. (2007) obtained bone marrow aspirates from 103 adults and children with acute leukemia at the time of initial diagnosis or relapse. Ninety study participants received induction chemotherapy. Bone marrow aspirate samples were subjected to the MTT assay to determine chemosensitivity. There was no significant correlation between the MTT assay results and disease-free survival or overall survival. Differences of mean MTT dead cell percentages between samples taken at initial diagnosis and those at relapse were not statistically significant. In vitro chemosensitivity testing with the MTT assay predicted whether those with acute myelogenous leukemia achieved remission after induction chemotherapy and remained in continuous remission or relapsed, but not in those with acute lymphoblastic leukemia.

In a retrospective review using the MTS assay, O'Toole, et al. (2003) reported on the results of a correlational study involving 88 tumor samples of individuals undergoing surgery for carcinoma of the cervix, endometrium, or ovary. In vitro sensitivity data was provided to the physician; however, the selection of chemotherapy was decided by the oncologist. In most cases standard chemotherapy regimens were given. Retrospective correlations between chemosensitivity/resistance and clinical response were available in 45 of 88 cases. The authors note that the majority of correlations were for the ovarian cancer patients. In 15 cases the tumor was found to be resistant in vitro and in 14 of these cases the patient presented with a recurrence, had evidence of active disease or died from the disease, which suggests 93% prediction accuracy for resistance. In 30 instances the tumor was sensitive to a drug in vitro. Twenty-six of these patients were free of disease at the time of study publication. The authors note that this suggests 87% prediction accuracy for sensitivity and that the probability of a negative in vitro test for a patient who failed to respond clinically was 78%. Study limitations include non-randomized and retrospective design, and assumptions regarding cause of active disease, disease progression, or death. The authors note that randomized prospective trials are needed to validate study results.

Prospective randomized clinical comparative trial data demonstrating improved overall health outcomes utilizing assay-directed therapy compared to physician-directed/empiric-based therapy are required to demonstrate the clinical utility of this assay. Further, professional society/organizational consensus support in the form of published guidelines is lacking. At this time, the role of in vitro tumor chemosensitivity and chemoresistance assays has not been established.

Tumor Drug Response Testing (ChemoFx): Tumor Drug Response Testing (ChemoFx®, Helomics Pittsburgh, PA) is a live chemoresponse marker. It quantifies an individual cancer patient's probable tumor response to up to 12 various chemotherapeutic and biologic agents—providing both sensitivity and resistance information (Richard, et al., 2015). Small tissue samples from surgery may be tested. Cells are cultured in a growth medium in the laboratory over a period of time and subjected to chemotherapy drugs or drug combinations. Helomics is a part of Predictive Oncology (Predictive Oncology, Eagan Minnesota 2023). It is proposed that this assay can provide predictions of responses to specific agents alone or in combination. The level of cell kill is recorded for each drug across multiple doses.

Rutherford et al. (2013) reported results from a prospective, noninterventional, correlational cohort study involving women with persistent or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. Three hundred thirty-five women were enrolled and treated on one of 15 study protocols; 262 women had adequate follow-up data and a ChemoFX assay result. The primary endpoint was progression-free survival (PFS); overall survival (OS) was the secondary endpoint. Cancer cells were classified as sensitive, intermediate or resistant to each of several chemotherapy regimens. Chemotherapy was selected by the treating physician who was blinded to assay results for the initial protocol treatment. PFS for patients treated with an assay sensitive regimen was a median of 8.8 months compared with 5.9 months for those with an assay-intermediate or resistant regimen (p=0.009). Mean overall survival was 37.5 months and 23.9 months for patients treated with an assay-sensitive regimen compared with an assay-intermediate or -resistant regimen, respectively (p=0.010). Study limitations include lack of randomization and non-interventional study design.

In a subsequent study, Tian et al. (2014) analyzed the assay's ability to predict PFS rates based on further analysis of the Rutherford study (2013). The association to PFS when the assayed therapy matched the administered therapy (match) was compared with the results when the assayed therapy was randomly selected, not necessarily matching the administered therapy (mismatch). The authors stated that the assay has predictive value because improved PFS was

associated with the administration of an assay-sensitive therapy. Although results of this correlational study suggest a significant association of chemosensitive-assay results with PFS, prospective, interventional studies are needed to determine whether clinical outcomes are improved by the use of this test compared to therapy selected by empirical methods.

Huh et al. (2011) reported response rates of 755 endometrial specimens using the Chemo FX assay. An average of four chemotherapy regimens was tested for each specimen. The in vitro response rates were compared with population response rates. Although response rates reflected by assay results were generally consistent with published population rates, uncontrolled study design and the lack of comparison of the ChemoFx prediction of response and actual patient outcomes are limitations of the study.

Herzog et al. (2010) attempted to determine if there was an association between tumor responses in vitro to platinum therapy by comparing the ChemoFx drug response marker and overall survival (OS) after first-line platinum-based chemotherapy in 192 individuals with advanced-stage primary ovarian cancer. One hundred and forty-seven participants were included in another clinical trial publication. Date of death was determined by an independent epidemiologist consultant, who was blinded to the ChemoFx results. The average number of different drugs or combinations ordered by the physician and tested by using ChemoFx was 8.9. The majority of tumors were tested for, and showed response to, platinum compounds. Scores were classified as responsive, intermediately responsive, or non-responsive. Patients receiving a responsive or intermediately responsive drug had significantly longer OS than patients receiving a non-responsive drug ($p=0.0386$). The ChemoFx score significantly associated with OS ($p=0.023$). Final treatment decisions were made by the patient's physicians. It is unknown the extent to which test results influenced clinical decision making; therefore the clinical utility of this test cannot be determined.

In a feasibility study, Mi et al. (2008) tested expanded tumor cells from biopsies of 62 breast lesions for chemoresponse using the ChemoFx assay. Pathologic complete response was determined in 34 individuals. In a limited initial patient outcome correlation, assay score of docetaxel/capecitabine significantly predicted pathologic complete response. The cross-validated model accuracy rate was 75%.

In an effort to determine the effectiveness of ChemoFx in predicting response to chemotherapy measured in progression-free interval, Gallion et al. (2006) reported results of a retrospective study of 317 patients with ovarian tumors. Specimens from surgically excised ovarian carcinomas were submitted for testing via the ChemoFx assay. A statistically significant correlation between assay prediction of response and PFI was observed in 256 cases with an exact or partial match between drug(s) assayed and received. This study was limited by retrospective design and the lack of a control group for comparison.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

ChemoID® Drug Response Assay:R ChemoID® is a chemo-sensitivity test for both cancer stem cells and bulk tumor cells. ChemoID testing starts with a small tumor and involves growing bulk tumor cells and enrichment of cancer stem cells. Those cells then are treated with various standard of care FDA approved chemotherapeutic agents to determine how many tumor-derived cells and cancer stem cells (CSCs) are killed using each drug or combinations of drugs. A response curve is generated for each drug evaluated, and the data are presented graphically as the cytotoxic index for the oncologist.

Howard et al. (2017) conducted a prospective study evaluating the use of the ChemoID drug response assay in glioblastoma (GBM) patients treated with standard of care. ChemoID is a drug response assay proposed to identify the most effective chemotherapy against cancer stem cells (CSCs) and bulk of tumor cells from a panel of potential treatments. The investigational cohort study was designed to examine utility and inform power calculations for a proposed larger follow-up randomized clinical trial. Patients were included in the study if they were age ≥ 18 years, clinically diagnosed with GBM and had surgical biopsy for the ChemoID assay. Patients (n=41) were all eligible for a surgical biopsy, and fresh tissue samples were collected for drug sensitivity testing. Patients were treated with standard-of-care temozolomide (TMZ) plus radiation with or without maximal surgery, depending on the status of the disease. Patients and physicians were blinded to the assay results. Patients were prospectively monitored for tumor response, time to recurrence, progression-free survival (PFS), and overall survival (OS). Odds ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes were estimated for CSC, bulk tumor, and combined assay responses for the standard-of-care TMZ treatment. Additionally, sensitivities/specificities, areas under the curve (AUCs), and risk reclassification components were examined. Follow-up occurred every three months during the treatment, every three months for the first year, and every three to six months thereafter. For every 5% increase in in vitro CSC cell kill by TMZ, the 12-month patient response (non-recurrence of cancer) increased two-fold (p=0.016). TMZ bulk tumor %-cell kill was similarly associated but with less statistical support (p=0.066). Combining CSC and bulk tumor assay results in a single model yielded a statistically supported CSC association (p=0.036) but the bulk tumor test association was not significant (p=0.472). Related optimal thresholds for the assays were 40% CSC cell kill and 55% bulk tumor cell kill by TMZ which then provided sensitivities/specificities of 100/97, 100/89, and 100/97, respectively for the CSC only, bulk tumor only, and combined models. Risk categorization of patients was improved by 11% when using the CSC test in conjunction with the bulk test (p=0.030). Median recurrence time was 20 months for patients with a positive (> 40% cell kill) CSC test versus only three months for those with a negative CSC test, whereas median recurrence time was 13 months versus four months for patients with a positive (> 55% cell kill) bulk test versus negative. Similar favorable results for the CSC test were observed for PFS and OS outcomes. Panel results across 14 potential other treatments indicated that 34/41 (83%) potentially more optimal alternative therapies may have been chosen using CSC results, whereas 27/41 (66%) alternative therapies may have been chosen using bulk tumor results. Patients with positive ChemoID CSC tests (> 40% cell kill) had longer median times to recurrence (20 months) than those with negative CSC tests (three months). Patients with positive bulk tumor tests (> 55% cell kill) had longer median times to recurrence (13 months) than those with negative bulk tumor tests (four months). The authors concluded that the ChemoID CSC drug response assay has the potential to increase the accuracy of bulk tumor assays to help guide individualized chemotherapy choices. However, larger trials are needed to determine the validity of ChemoID drug response assay directed toward CSCs, which contribute to tumor propagation, maintenance, and treatment resistance.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Microculture Kinetic Assay of Apoptosis (e.g., CorrectChemo, formerly MiCK®): This assay determines the extent of apoptosis, or cell death, in a population of cells after exposure to cytotoxic agents. The assay is proposed for use for an individual patient prior to the initiation of a chemotherapy drug or drugs in treatment.

Strickland et al. (2013) reported outcomes of a prospective observational correlational study reporting the results of the MiCK® assay regarding the rate of apoptosis in cells from blood or bone marrow aspirate of 109 adults with previously untreated acute myeloid leukemia. The study

spanned 14 years beginning in 1996 through 2010 and involved two patient cohorts. The rate of apoptosis for each drug as noted by the MiCK® assay was significantly correlated with the complete response and overall survival rates for each individual for chemotherapy drugs noted to have greater apoptosis activity. Use of the MiCK® assay did not change clinical management as the chemotherapy regimen was selected by the treating physician based on best medical practice/standard of care and the treating physician was blinded to MiCK® assay results.

Salom et al. (2012) reported results of a prospective, nonrandomized observational trial to determine if a chemotherapy-induced apoptosis assay (MiCK) could predict the best therapy for 104 evaluable patients with ovarian cancer. Patients with epithelial ovarian cancer of any stage, primary or recurrent, were eligible. Overall survival in primary therapy, chemotherapy naïve patients with Stage III or IV disease was longer if patients received a chemotherapy which was best in the MiCK assay, compared to shorter survival in patients who received a chemotherapy that was not the best ($p<0.01$, hazard ratio [HR] 0.23). Multivariate model risk ratio showed use of the best chemotherapy in the MiCK assay was the strongest predictor of overall survival ($p<0.01$) in stage III or IV patients. Relapse-free interval in primary therapy patients was longer if patients received the best chemotherapy from the MiCK assay ($p=0.03$, HR 0.52). Response rates were higher if physicians used an active chemotherapy based on the MiCK assay ($p=0.03$). Study limitations included uncontrolled trial design and short-term follow-up.

Bosserman et al. (2012b) reported results of an observational prospective nonblinded clinical trial in 44 patients with breast cancer (n=16), non-small cell lung cancer (n=6), non-Hodgkin lymphoma (n=4) and other diagnoses to determine the effect of a drug-induced apoptosis assay results on treatment planned by oncologists. Patients with cancer of any stage, primary or recurrent, were eligible. Four patients received adjuvant chemotherapy after MiCK, and 40 received palliative chemotherapy. There were no rules or directions regarding how to use the MiCK assay results. The study evaluated whether the oncologist used the results of the assay, other data were also used (e.g., estrogen receptor analysis or human epidermal growth receptor 2 [HER2] test results, or addition of other drugs), or whether the assay results were not used. Oncologists used the MiCK assay to determine chemotherapy users in 28 (64%) and did not (nonusers) in 16 patients (36%). In users receiving palliative chemotherapy, complete plus partial response rate was 44%, compared with 6.7% in nonusers ($p<0.02$). The median overall survival was 10.1 months in users versus 4.1 months in nonusers ($p=0.02$). Relapse-free interval was 8.6 months in users versus 4.0 months in nonusers ($p<0.01$). Limitations include uncontrolled study design, short follow-up, and small patient populations.

Ballard et al. (2010) reported results of a study of 19 individuals with endometrial cancer. Tumors were analyzed with the MiCK assay against various single and combination chemotherapy regimens to determine chemosensitivity responsiveness for 15 individuals. Assay results of study participants were compared to clinical response rates of participants of previously completed Gynecologic Oncology Group (GOG) trials. There was correlation between the demonstrated activity of the chemotherapy regimens used in vivo GOG trials and the chemosensitivity of tumor samples used for the MiCK assay ($p<0.0328$). According to the authors, the results indicate that 25% of study participants might be treated with single agent chemotherapy selected by the MiCK assay, although this prediction is based on wide confidence intervals because of the small number of samples.

There is insufficient evidence to demonstrate the impact of microculture kinetic assay of apoptosis (MiCK) on the clinical management of the patient. Whether outcomes are improved compared with management based on best current therapy/standard of care is not known; the use of in vitro assays to detect chemosensitivity has not yet been translated into routine clinical practice. The ability of these tests to identify active and inactive chemotherapy agents in the laboratory setting does not necessarily translate into a clinically useful prediction of response to therapy and patient

survival as demonstrated by outcomes in high-quality, controlled clinical trials. Data are not robust; peer-reviewed published data are primarily observational, correlational studies. Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Flow Cytometric Chemosensitivity Assay (FCCA): In FCCA, cryopreserved cells are thawed, washed, re-suspended, and added to a specific chemotherapy drug or drug combinations in various drug concentrations.

Galderis et al. (2009) studied the relationship between in vitro drug sensitivity of diagnostic leukemic blasts from 30 children with acute lymphoblastic leukemia (ALL) and the rapidity of response to induction therapy. Study participants were enrolled on Children's Oncology Group clinical trials from 1997 to 2007. Five drugs were each tested at three concentrations. The in vitro drug sensitivity of de novo leukemic blasts among various clinical subsets was also tested. Cellular drug response was determined successfully by FCCA in 30 of 38 samples analyzed. Slow early response to induction therapy was associated with a significantly increased lymphoblast survival after exposure to glucocorticoid therapy in vitro. Limitations of the study include small sample size, the lack of exposing blasts simultaneously to multiple induction drugs as occurs with in vivo treatment, and the failure to account for potential drug synergism.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Adenosine Triphosphate (ATP) Chemotherapy Response Assay: In this technique, tumor cells are isolated and subjected to multiple single drug and combination drug therapies at increasing drug concentrations.

Chen et al. (2018) evaluated the in vitro chemosensitivity and multiple drug resistance (MDR) of tumor tissues from 120 lung cancer patients to eight single-drug chemotherapies and of 291 lung cancer patients to seven chemotherapy regimens using an ATP-based tumor chemosensitivity assay. Results reflected differences in the sensitivity of different tumor types to chemotherapeutic drugs. The researchers noted some limitations to the study: the growth environment of in vitro-cultured tumor cells is different from that in vivo, the success rate of in vitro tumor cell culture is low, the in vitro-measured sensitivity cannot provide information on the toxicity of drugs in normal tissues and in vitro tumor cells lack the metabolic functions of host cells. These methods leave room for improvement. The authors of the study also noted the mechanism of resistance and the strategies to reverse drug resistance remain to be elucidated.

Hur et al. (2012) reported outcomes of a randomized clinical trial designed to determine effectiveness of adenosine triphosphate-based chemotherapy response assay (ATP-CRA)-guided neoadjuvant chemotherapy for increasing resectability in 63 patients with unresectable colorectal liver metastasis. Patients were randomized into two groups: Group A (n=32) was treated by conventional chemotherapy regimen and Group B (n=31) was treated by chemotherapy regimen according to the ATP-CRA. Treatment response and resectability were compared between Group A and B. Median follow-up was 12 months. Group B showed better treatment response than group A (48.4% versus 21.9%, p=0.027). The resectability of the hepatic lesion was significantly higher in Group B than in Group A (35.5% versus 12.5%, p=0.032). According to multivariate logistic regression analysis, ATP-CRA was significantly associated with good treatment response (p=0.004) and liver resection (p=0.009). Data suggest improved resectability with use of the ATP response assay in this patient group; however, additional well designed RCTs are needed to determine applicability into routine clinical practice.

Kim et al. (2010) assessed the accuracy of ATP-CRA using clinical response as a reference standard in 48 individuals with chemo-naïve, locally advanced or metastatic gastric cancer. Thirty-six individuals had evaluable results. The chemosensitivity index method yielded an accuracy of 77.8%. Specificity, sensitivity, and negative and positive predictive values were 95.7%, 46.2%, 85.7%, and 75.9%, respectively. The in vitro chemosensitivity group showed higher response rates (85.7% versus 24.1%, p=0.005) compared with the in vitro chemoresistant group.

Cree et al. (2007) conducted a prospective randomized controlled trial to determine the response rate and progression-free survival following chemotherapy in patients with ovarian cancer who had been treated according to a tumor chemosensitivity assay in comparison with physician's choice. A total of 180 patients were randomized, with 94 receiving assay-directed treatment and 86 receiving physician's choice therapy. Evidence of response was not significantly different between the two groups (p<0.3). Additionally, there was no significant difference in the median progression free- or overall survival between the two groups, (p<0.14 and p<0.8, respectively), although there was a trend towards improved response and progression-free survival for assay-directed treatment.

Ugurel et al. (2006) reported outcomes of a multicenter phase II randomized controlled trial investigating the efficacy of assay-directed, first-line chemotherapy for patients with melanoma who had no distinct alterative to empirical therapy. ATP assay was used for patients with metastasis. The study groups were divided into 22 chemotherapy-sensitive patients and 31 chemotherapy-resistant patients. Objective response and OS were 36.4% and 14.6 months, respectively, in the chemotherapy-sensitive group, and 16.1% and 7.4 months, respectively, in the chemotherapy resistant group. There was no comparison between the two therapeutic interventions.

Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Histoculture Drug Response Assay (HDRA): HDRA is a type of test evaluating cell death, or apoptosis. Tumor specimens are minced and plated in the presence of single drug or drug combinations. After histoculture, specimens are analyzed for cell death by inhibition rate.

In a correlation study Lee et al. (2012) reported sensitivity of fresh tumor samples from 79 patients with epithelial ovarian cancer to 11 chemotherapy agents. Retrospective analysis was performed. Among the 37 patients with International Federation of Gynecology and Obstetrics (FIGO) stage III/IV serous adenocarcinoma who were receiving carboplatin combined with paclitaxel, those with carboplatin-sensitive samples on HDRA had a significantly longer median disease-free interval than patients with carboplatin-resistant samples (p<0.05), but median overall survival did not differ significantly (p=0.621). In a study analyzing results using the HDRA in a case series study involving 173 patients and 164 evaluable tumors, Nakada et al. (2005) reported a true-positive rate of 90%, true-negative of 78.9%, and overall accuracy of 82.8%.

Further evaluation is warranted to confirm the relationship between results of the histoculture drug response assay (HDRA) and clinical responses. Prospective randomized clinical trial data comparing assay-directed therapy with empiric-based therapy are required to demonstrate improved patient survival. At this time the clinical utility of this assay has not been established.

Ex vivo 3D cell culture/Reverse Phase Protein Array (RPPA): Ex vivo 3D cell culture platforms use live cancer cells from surgical or biopsy specimens to create a patient-specific in vivo-like tumor that is used to predict response to approved and investigational cancer drugs. This

technique uses in vitro assessment of drug-on-tumor cell interaction prior to in vivo therapy administration. RPPA measures the abundance and activation of cell surface receptor proteins and their downstream signaling pathways. These biomolecules serve as the drug targets for most FDA-approved and investigational therapies for cancer. RPPA is proposed to prevent the patient from being exposed to cytotoxic treatments that might not achieve clinically benefits, while guiding physicians to prescribe treatments that are likely to be therapeutic.

Shuford et al. (2021) conducted a prospective study that assessed if an ex vivo 3D cell culture assay could predict clinical drug response in high-grade gliomas (HGC). Clinical correlation was determined between prospective ex vivo response and clinical response in newly diagnosed (ND) HGG patients enrolled in 3D-PREDICT. The 3D-PREDICT REGISTRY is an observational clinical study evaluating patient-specific ex vivo 3D (EV3D) assay for drug response using a patient's own biopsy or resected tumor tissue for assessing tissue response to therapy in patients with advanced cancers, including ovarian cancer, high-grade gliomas, and high-grade rare tumors. A modified 3D cell culture assay was validated to establish baseline parameters including drug concentrations, timing, and reproducibility. Live tumor tissue from HGG patients (n=44) were tested in the assay to establish prospective ex-vivo response parameters. Clinical correlation was determined between prospective ex vivo response and clinical response in ND HGG patients enrolled in 3D-PREDICT. Out of 107 samples assayed, 33 tissue samples were successfully assayed for categorical response to temozolomide (TMZ) and up to 11 other compounds, per the 3-D PREDICT protocol. Of the 33 patients, 20 progressed at the time of this analysis to compare their clinical response to the test response. Clinical data were collected for each patient during follow-up visits at approximately three month intervals. In all cases chemotherapeutic agent selection was guided by the neuro-oncologist’s clinical judgement. For recurrent patients, the clinician considered a combination of the following factors: patient’s age, performance status, comorbidities, toxicities/side effect profile of potential chemotherapy agents, and results of the 3D Predict Glioma assay. For the purposes of this study, progression free survival (PFS) and overall survival (OS) were both defined from the time of surgical resection to the time of measured progression or death. Clinical progression was defined by radiographic progression as interpreted by the treating clinicians. Absent biomarker stratification, the test accurately predicted clinical response/nonresponse to TMZ in 17/20 (p=0.007) ND patients within seven days of their surgery, prior to treatment initiation. Test predicted-responders had a median overall survival post-surgery of 11.6 months (4.2–30.4) compared to 5.9 months (3.3–11.7) for test predicted non-responders (p=0.0376). The authors noted that future development to reduce required tissue amounts for assay performance may increase the number of patients able utilize the assay. Additionally, large, randomized controlled trials will provide better evidence of the assay’s usefulness. No health disparities were identified by the investigators.

Summary for Chemosensitivity and Chemoresistance Assays (CSRAs): Prospective randomized clinical trial data are lacking to evaluate overall survival of individuals treated with assay-directed regimens compared with controls treated with an empiric regimen. The evidence regarding CSRAs is primarily derived from correlational trials that do not use intent-to-treat analysis or investigate survival rates. A majority of studies do not assess overall survival as a primary endpoint which limits the clinical utility of the test (Ferriss, 2010). Additionally, optimal dosing, treatment regimens, and specific patient selection criteria should be determined. Although they remain an active focus of research, data are insufficient to demonstrate an improvement of health outcomes. At this time in vitro chemosensitivity and chemoresistance assays have not been established as a standard of practice in the clinical setting.

U.S. Food and Drug Administration (FDA): While laboratories that perform in vitro chemosensitivity and chemoresistance testing are regulated by the FDA under the Clinical Laboratory Improvement Amendments (CLIA), the FDA does not typically directly clear or approve individual tests. Lab-developed tests go to market without independent analysis.

Professional Societies/Organizations
American Society of Clinical Oncology (ASCO): On behalf of the ASCO Working Group, Burstein et al. (2011) published updated recommendations on the use of chemotherapy sensitivity and chemoresistance assays to select chemotherapeutic agents for individual patients. According to the Practice Guideline "The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations based on published reports of clinical trials and a patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority."

National Comprehensive Cancer Network® (NCCN®): The NCCN clinical practice guideline for ovarian cancer/fallopian tube cancer/primary peritoneal cancer (2025) noted that chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN centers to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; however, the current level of evidence is not sufficient to supplant standard of care chemotherapy (category 3 recommendation). The NCCN panel noted that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3 recommendation), owing to the lack of demonstrable efficacy for such an approach.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Human Tumor Stem Cell Drug Sensitivity Assays (190.7)	7/1/1996
LCD	Palmetto GBA	In Vitro Chemosensitivity & Chemoresistance Assays (L34554)	7/11/2024
LCD	Noridian Healthcare Solutions, LLC	In Vitro Chemosensitivity & Chemoresistance Assays (L37630)	2/25/2020
LCD	Noridian Healthcare Solutions, LLC	In Vitro Chemosensitivity & Chemoresistance Assays (L37628)	2/25/2021

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
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; each additional single drug or drug combination (List separately in addition to code for primary procedure)
0174U	Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents
0248U	Oncology, spheroid cell culture in a 3D microenvironment, 12-drug panel, brain- or brain metastasis-response prediction for each drug
0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report
0525U	Oncology, spheroid cell culture, 11-drug panel (carboplatin, docetaxel, doxorubicin, etoposide, gemcitabine, niraparib, olaparib, paclitaxel, rucaparib, topotecan, veliparib) ovarian, fallopian, or peritoneal response prediction for each drug
0564T	Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported based on percent of cytotoxicity observed, a minimum of 14 drugs or drug combinations (Code deleted 12/31/2024)

References

1. Ballard KS, Homesley HD, Hodson C, Presant CA, Rutledge J, Hallquist A, et al. Endometrial carcinoma in vitro chemosensitivity testing of single and combination chemotherapy regimens using the novel microculture kinetic apoptosis assay: implications for endometrial cancer treatment. J Gynecol Oncol. 2010 March;21(1):45-9.

2. Blom K, Nygren P, Larsson R, Andersson CR. Predictive Value of Ex Vivo Chemosensitivity Assays for Individualized Cancer Chemotherapy: A Meta-Analysis. SLAS Technol. 2017 Jun;22(3):306-314.

3. Bosanquet AG, Richards SM, Wade R, Else M, Matutes E, Dyer MJ, et al. drug Cross-resistance and therapy-induced resistance in chronic lymphocytic leukaemia by an enhanced method of individualised tumor response testing. Br J Haematol. 2009 Aug;146(4):384-95.

4. Bosserman L, Prendergast F, Herbst R, Fleisher M, Salom E, Strickland S, et al. The microculture-kinetic (MiCK) assay: the role of a drug-induced apoptosis assay in drug development and clinical care. Cancer Res. 2012a Aug 15;72(16):3901-5.

5. Bosserman LD, Rajurkar SP, Rogers K, Davidson DC, Chernick M, Hallquist A, et al. Correlation of drug-induced apoptosis assay results with oncologist treatment decisions and patient response and survival. Cancer. 2012b Oct 1;118(19):4877-83.

6. Bosserman L, Rogers K, Willis C, Davidson D, Whitworth P, Karimi M, et al. Application of a drug-induced apoptosis assay to identify treatment strategies in recurrent or metastatic breast cancer. PLoS One. 2015 May 29;10(5):e0122609.

7. Burstein HJ, Mangu PB, Somerfield MR, Schrag D, Samson D, Holt L, et al. American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. J Clin Oncol. J Clin Oncol. 2011 Aug 20;29(24):3328-30.

8. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Mar 12, 2025. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/local-coverage-final-lcds-alphabetical-report.aspx?lcdStatus=all

9. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Mar 12, 2025. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncd-report.aspx?chapter=all&sortBy=title

10. ChemoID®. Copyright © 2024 ChemoID. Accessed Mar 12, 2025. Available at URL address: https://chemoid.com/for-physicians/

11. Chen Z, Zhang S, Ma S, Li C, Xu C, Shen Y, et al. Evaluation of the in vitro Chemosensitivity and Correlation with Clinical Outcomes in Lung Cancer using the ATP-TCA. Anticancer Agents Med Chem. 2018;18(1):139-145.

12. Cloven NG, Kyshtoobayeva A, Burger RA, Yu I-R, Fruehauf JP. In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer. Gynecol Oncol. 2004 Jan;92(1):160-6.

13. Cortese A, Pantaleo G, Amato M, Lawrence L, Mayes V, Brown L, et al. A new complementary procedure for patients affected by head and neck cancer: Chemo-predictive assay. Int J Surg Case Rep. 2016;26:42-6.

14. Cree IA, Kurbacher CM, Lamont A, Hindley AC, Love S, TCA Ovarian Cancer Trial Group. A prospective randomized controlled trial of tumour chemosensitivity assay directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer. Anticancer Drugs. 2007 Oct;18(9):1093-101.

15. Cross SN, Cocco E, Bellone S, Anaqnostou VK, Brower SL, Richter CE, et al. Differential sensitivity to platinum-based chemotherapy in primary uterine serous papillary carcinoma cell lines with high vs low HER-2/neu expression in vitro. Am J Obstet Gynecol. 2010 Aug;203(2):162.e1-8.

16. D'Arcangelo M, Todaro M, Salvini J, Benfante A, Colorito ML, D'Incecco A, et al. Cancer Stem Cells Sensitivity Assay (STELLA) in Patients with Advanced Lung and Colorectal Cancer: A Feasibility Study. PLoS One. 2015 May 8;10(5):e0125037.

17. Des Guetz G, Schischmanoff O, Nicolas P, Perret GY, Morere JF, Uzza B. Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analyses. Eur J Cancer. 2009 Jul;45(10):1890-6.

18. Ferriss JS, Rice LW. The role of in vitro directed chemotherapy I epithelial ovarian cancer. Rev Obstet Gynecol. 2010 Spring;392):49-54.

19. Galderisi F, Stork L, Li J, Mori M, Mongoue-Tchokote S, Huang J. Flow cytometric chemosensitivity assay as a predictive tool of early clinical response in acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009 Oct;53(4):543-50.

20. Gallion H, Christopherson WA, Coleman RL, Demars L, Herzog T, Hosford S, et al. Progression-free interval in ovarian cancer and predictive value of an ex vivo chemoresponse assay. Int J Gynecol Cancer. 2006;16:194-201.

21. Grigsby PW, Zighelboim I, Powell MA, Mutch DG, Schwarz JK. In vitro chemoresponse to cisplatin and outcomes in cervical cancer. Gynecol Oncol. 2013 Jul;130(1):188-91.

22. Harry VM, Gilbert FJ, Parkin DE. Predicting the response of advanced cervical and ovarian tumors to therapy. Obstet Gynecol Surv. 2009 Aug;64(8):548-60.

23. Havrilesky LJ, Krivak TC, Mucenski JW, Myers ER. Impact of a chemoresponse assay on treatment costs for recurrent ovarian cancer. Am J Obstet Gynecol. 2010 Aug;203(2): 106.e1-7.

24. Herzog TJ, Krivak TC, Fader AN, Coleman RL. Chemosensitivity testing with ChemoFX and overall survival in primary ovarian cancer. Am J Obstet Gynecol. 2010 Jul;203(1):68.e1-6. Epub 2010 Mar 12.

25. Howard CM, Bush S 2nd, Zgheib NB, Lirette ST, Cortese A, Mollo A, Valluri J, Claudio PP. Cancer Stem Cell Assay for the Treatment of Platinum-Resistant Recurrent Ovarian Cancer. HSOA J Stem Cells Res Dev Ther. 2021;7(3):076.

26. Howard CM, Zgheib NB, Bush S 2nd, DeEulis T, Cortese A, Mollo A, et al. Clinical relevance of cancer stem cell chemotherapeutic assay for recurrent ovarian cancer. Transl Oncol. 2020 Dec;13(12):100860.

27. Howard CM, Valluri J, Alberico A, Julien T, Mazagri R, Marsh R, et al. Analysis of Chemopredictive Assay for Targeting Cancer Stem Cells in Glioblastoma Patients. Transl Oncol. 2017 Apr;10(2):241-254.

28. Huh WK, Cibull M, Gallion HH, Gan CM, Richard S, Cohn DE. Consistency of in vitro chemoresponse assay results and population clinical response rates among women with endometrial carcinoma. Int J Gynecol Cancer. 2011 Apr;21(3):494-9.

29. Hur H, Kim NK, Kim HG, Min BS, Lee KY, Shin SJ, et al. Adenosine triphosphate-based chemotherapy response assay-guided chemotherapy in unresectable colorectal liver metastasis. Br J Cancer. 2012 Jan 3;106(1):53-60.

30. Isacoff WH, Cooper B, Bartlett A, McCarthy B, Yu KH. ChemoSensitivity Assay Guided Metronomic Chemotherapy Is Safe and Effective for Treating Advanced Pancreatic Cancer. Cancers (Basel). 2022 Jun 13;14(12):2906.

31. Joo WD, Lee JY, Kim JH, Yoo HJ, Roh HJ, Park JY, et al. Efficacy of taxane and platinum-based chemotherapy guided by extreme drug resistance assay in patients with epithelial ovarian cancer. J Gynecol Oncol. 2009 Jun;20(2):96-100.

32. Jun KR, Jang S, Chi HS, Lee KH, Lee JH, Choi SJ, et al. Relationship between chemosensitivity assessed with MTT assay and clinical outcomes in 103 patients with acute leukemia. Korean J Lab Med. 2007 Apr;27(2):89-95.

33. Karam AK, Chiang JW, Fug E, Nossaov V, Karlan BY. Extreme drug resistance assay results do not influence survival in women with epithelial ovarian cancer. Gynecol. Oncol. 2009 Aug;114(2):246-52.

34. Kim JH, Lee KW, Kim YH, et al. Individualized tumor response testing for prediction of response to paclitaxel and cisplatin chemotherapy in patients with advanced gastric cancer. J Korean Med Sci. 2010;25(5):684-690

35. Kim SW, Kim YM, Kim MB, Kim DY, Kim JH, Nam JH, et al. Chemosensitivity of uterine cervical cancer demonstrated by the histoculture. Tohoku J Exp Med. 2009 Dec;219(4):277-82.

36. Kiyatec 3D Predict™. © 2025 Kiyatec. Accessed Mar 12, 2025. Available at URL address: https://kiyatec.com/

37. Ledford A, Rodriguez A, Lipinski L, Abad A, Fenstermaker R, Edenfield J, Kanos C, Redjal N, Mansouri A, Zacharia B, Butowski N, Liu J, Han SJ, Ziu M, Cohen AL, Fabiano AJ, Miles K, Rayner M, Thompson J, Tollison K, Azimzadeh P, Holmes L, Gevaert M, DesRochers TM. Functional prediction of response to therapy prior to therapeutic intervention is associated with improved survival in patients with high-grade glioma. Sci Rep. 2024 Aug 29;14(1):19474.

38. Lee SW, Kim YM, Kim MB, Kim JH, Nam JH, Kim YT. In vitro chemosensitivity using the histoculture drug response assay in human epithelial ovarian cancer. Acta Med Okayama. 2012 Jun;66(3):271-7.

39. Loizzi V, Chan JK, Osann K, Cappuccini F, DiSaia PJ, Berman ML. Survival outcomes in patients with recurrent ovarian cancer who were treated with chemoresistance assay-guided chemotherapy. Am j Obstet Gynecol. 2003 Nov;189(5):1301-7.

40. Lyons JM III, Abergel J, Thomson JL, Anthony CT, Wang YZ, Anthony YB, et al. In vitro chemoresistance testing in well-differentiated carcinoid tumors. Ann Surg Oncol. 2009 Mar;16(3):649-55.

41. Marcolin JC, Lichtenfels M, da Silva CA, de Farias CB. Gynecologic and Breast Cancers: What's New in Chemoresistance and Chemosensitivity Tests? Curr Probl Cancer. 2023 Aug;47(4):100996.

42. Matsuo K, Bond VK, Im DD, Rosenshein NB. Prediction of chemotherapy response with platinum and taxane in the advanced stage of ovarian and uterine carcinosarcoma: a clinical implication of in vitro drug resistance assay. Am J Clin Oncol. 2010 Aug;33(4):358-63.

43. Matsuo K, Eno ML, Im DD, Rosenshein NB, Sood AK. Clinical relevance of extent of extreme drug resistance in epithelial ovarian carcinoma. Gynecol Oncol. 2010 Jan;116(1):61-5.

44. Mi Z, Holmes FA, Hellerstedt B, Pippen J, Collea R, Backner A, et al. Feasibility assessment of a chemoresponse assay to predict pathologic response in neoadjuvant chemotherapy for breast cancer patients. Anticancer Res. 2008 May-Jun;28(3B):1733-40.

45. Nakada S, Aoki D, Ohie S, Horiuchi M, Suzuki N, Kanasugi M, et al. Chemosensitivity testing of ovarian cancer using the histoculture drug response assay: sensitivity to cisplatin and clinical response. Int J Gynecol Cancer. 2005 May-Jun;15(3):445-52.

46. National Comprehensive Cancer Network® (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2025. Mar 5, 2025. Accessed Mar 12, 2025. Available at URL address: https://www.nccn.org/guidelines/category_1

47. O'Toole SA, Sheppard BL, Bonnar JB, McGuinness EPJ, Gleeson NC, Yoneda M. The MTS assay as an indicator of chemosensitivity/resistance in malignant gynecological tumors. Cancer Detect Prev. 2003;27(1):47-54.

48. Perian Biosciences. ChemoINTEL™. Accessed Mar 12, 2025. Available at URL address: https://www.pierianbio.com/products/chemointel/

49. Predictive Oncology. © 2023. Tumor drug-response & genomic biomarker testing (ChemoFx® from Helomics). Accessed Mar 12, 2025. Available at URL address: https://predictive-oncology.com/tumor-drug-response-genomic-biomarker-testing/

50. Ranjan T, Sengupta S, Glantz MJ, Green RM, Yu A, Aregawi D, Chaudhary R, Chen R, Zuccarello M, Lu-Emerson C, Moulding HD, Belman N, Glass J, Mammoser A, Anderson M, Valluri J, Marko N, Schroeder J, Jubelirer S, Chow F, Claudio PP, Alberico AM, Lirette ST, Denning KL, Howard CM. Cancer stem cell assay-guided chemotherapy improves survival of patients with recurrent glioblastoma in a randomized trial. Cell Rep Med. 2023 May 16;4(5):101025.

51. Richard S, Wells A, Connor J, Price F. Use of ChemoFx® for Identification of Effective Treatments in Epithelial Ovarian Cancer. PLoS Curr. 2015 Jul 13;7:ecurrents.eogt.8b0b6fffc7b999b34bc4c8152edbf237.

52. Rutherford T, Orr J Jr, Grendys E Jr, Edwards R, Krivak TC, Holloway R, et al. A prospective study evaluating the clinical relevance of a chemoresponse assay for treatment of patients with persistent or recurrent ovarian cancer. Gynecol Oncol. 2013 Nov;131(2):362-7.

53. Samson DJ, Seidenfeld J, Ziegler K, Aronson N. Chemotherapy sensitivity and resistance assays: a systematic review. J Clin Oncol. 2004;22(17):3618-30.

54. Salom E, Penalver M, Homesley H, Burrell M, Garrett A, Presant CA, et al. Correlation of pretreatment drug induced apoptosis in ovarian cancer cells with patient survival and clinical response. J Transl Med. 2012 Aug 8;10:162.

55. Schink JC, Copeland LJ. Point: chemosensitivity assays have a role in the management of recurrent ovarian cancer. J Natl Compr Canc Netw. 2011 Jan;9(1): 115-20.

56. Schrag D, Garewal HS, Burstein HJ, Samson DJ, Von Hoff DD, Somerfield MR, et al. American Society of Clinical Oncology Technology Assessment: Chemotherapy sensitivity and resistance assays. J Clin Oncol. 2004 Sep;22(17):3631-8.

57. Shuford S, Lipinski L, Abad A, Smith AM, Rayner M, O'Donnell L, et al. Prospective prediction of clinical drug response in high-grade gliomas using an ex vivo 3D cell culture assay. Neurooncol Adv. 2021 May 7;3(1):vdab065.

58. Strickland SA, Raptis A, Hallquist A, Rutledge J, Chernick M, Perree M, et al. Correlation of the microculture-kinetic drug-induced apoptosis assay with patient outcomes in initial treatment of adult acute myelocytic leukemia. Leuk Lymphoma. 2013 Mar;54(3):528-34.

59. Suksawat M, Klanrit P, Phetcharaburanin J, Namwat N, Khuntikeo N, Titapun A, et al. In vitro and molecular chemosensitivity in human cholangiocarcinoma tissues. PLoS One. 2019 Sep 10;14(9):e0222140.

60. Tian C, Sargent DJ, Krivak TC, Powell MA, Gabrin MJ, Brower SL, et al. Evaluation of a chemoresponse assay as a predictive marker in the treatment of recurrent ovarian cancer: further analysis of a prospective study. Br J Cancer. 2014 Aug 26;111(5):843-50.

61. Ugurel S, Schadendorf D, Pfohler C, Neuber K, Thoelke A, Ulrich J, et al. In vitro drug sensitivity predicts response and survival after individualized sensitivity-directed chemotherapy in metastatic melanoma: a multicenter phase II trial of the Dermatologic Cooperative Oncology Group. Clin Cancer Res.2006;12(18):5454-63.

62. Wu B, Zhu JS, Zhang Y, Shen WM, Zhang Q. Predictive value of MTT assay as an in vitro chemosensitivity testing for gastric cancer: one institution's experience. World J Gastroenterol. 2008 May 21;14(19):3064-8.

63. Yoon YS, Kim JC. Recent applications of chemosensitivity tests for colorectal cancer treatment. World J Gastroenterol. 2014 Nov 28;20(44):16398-408.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• No clinical policy statement changes.	5/15/2025
Focused Review	• No clinical policy statement changes.	2/15/2025
Annual Review	• No clinical policy statement changes.	5/15/2024