



Medical Policy

In Vitro Chemoresistance and Chemosensitivity Assays

Table of Contents

- [Policy: Commercial](#)
- [Policy: Medicare](#)
- [Authorization Information](#)
- [Coding Information](#)
- [Description](#)
- [Policy History](#)
- [Information Pertaining to All Policies](#)
- [References](#)

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Related Policies

NA

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

In vitro chemoresistance assays, including but not limited to, Extreme Drug Resistance Assays, are considered [INVESTIGATIONAL](#).

In vitro chemosensitivity assays, including, but not limited to, the Histoculture Drug Response Assay, a fluorescent cytoprint assay, or the ChemoFx assay, are considered [INVESTIGATIONAL](#).

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.
Medicare HMO Blue SM	This is not a covered service.
Medicare PPO Blue SM	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code 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)

Description

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 cytopspin-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 uptake 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.

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.

Summary

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 biologic 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.

For individuals who have cancer who are initiating chemotherapy who receive chemoresistance assays, the evidence includes correlational observational studies. Relevant outcomes are overall survival (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 the effects of the technology on health outcomes.

For individuals who have cancer who are initiating chemotherapy who 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 comparing outcomes for patients managed using a chemosensitivity assay with those managed using standard care, including a randomized controlled trial. 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 to determine whether the clinical use of in vitro chemosensitivity testing leads to improvements in OS are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

Date	Action
9/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
9/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
9/2018	BCBSA National medical policy review. CorrectChemo assay removed from the second policy statement; intent of statements unchanged. 9/1/2018
10/2017	New references added from BCBSA National medical policy.
8/2016	New references added from BCBSA National medical policy.
1/2016	Clarified coding information.
6/2015	BCBSA National medical policy review. Investigational indications clarified. Effective 6/1/2015.
7/2014	New references added from BCBSA National medical policy.
5/2013	New references from BCBSA National medical policy.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
8/1/2011	Reviewed- Medical Policy Group– Hematology and Oncology. No changes to policy statements.
12/1/2010	New policy describing ongoing non-coverage.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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