Medical Coverage Policy | In Vitro Chemoresistance and Chemosensitivity Assays

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 01|22|2025

OVERVIEW

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.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans

In vitro chemosensitivity assays and chemoresistance assays are not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products

In vitro chemosensitivity assays and chemoresistance assays are considered not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are

a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

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

Methods Using Differential Staining/Dye Exclusion

- The Differential Staining Cytotoxicity assay relies on dye exclusion of live cells after mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation. Cells are then established in culture and treated with the drugs of interest at 3 dose levels; the middle (relevant) dose is that which could be achieved in therapy; 10-fold lower than the physiologically relevant dose; and 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.

- The Ex-Vivo Analysis of Programmed Cell Death (EVA/PCD®) assay (Rational Therapeutics) measures differential staining of cells after apoptotic and nonapoptotic cell death markers in tumor samples are 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. The samples are then agitated, cytospin-centrifuged, air-dried, and counterstained with hematoxylin and eosin. The endpoint of interest for this assay is cell death, as assessed by the number of cells differentially stained due to changes in cellular membrane integrity.

- 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. 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 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 uptake of radioactivity and sensitivity of the cells to the agent(s) of interest.

- 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. 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

- 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. 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

- The Adenosine Triphosphate (ATP) Bioluminescence assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, and then exposed to drugs. Following incubation with 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 that the tumor is resistant to the agent of interest.
- ChemoFX® (Helomics Corp., previously called Precision Therapeutics) assay also relies on quantifying ATP based on chemoluminescence. Cells must be grown in a monolayer rather than in a 3-dimensional matrix.

For individuals with cancer who are initiating chemotherapy and 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 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 versus 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 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.

CODING

The following codes are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

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 Effective 12/31/2024)

These code(s) can be used for the ChemoFx® (Helomics):

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)

There are no specific CPT codes for other assays. Claims should be filed with an unlisted code.

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services
Unlisted Procedures

PUBLISHED

Provider Update, March 2025
Provider Update, April 2024
Provider Update, November 2023
Provider Update, November 2022
Provider Update, November 2021

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