In Vitro Chemoresistance and Chemosensitivity Assays

Policy # 00288
Original Effective Date: 03/16/2011
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers in vitro chemoresistance assays, including, but not limited to, Extreme Drug Resistance assay, to be **investigational.***

Based on review of available data, the Company considers in vitro chemosensitivity assays, including, but not limited to, the Histoculture Drug Response Assay, a fluorescent cytoprint assay, the ChemoFX assay to be **investigational.***

Background/Overview

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. Cells are then established in culture and treated with the drugs of interest at three 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 four to six 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 three 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 and cytospin-centrifuged and, after air drying, counterstained with hematoxylin and eosin. The endpoint of interest for this assay is cell death, as assessed by observing the number of cells differentially stained due to changes in cellular membrane integrity.

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. 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 four days. After three days, tritiated thymidine is added. After 24 hours of additional incubation, cells are lysed, and radioactivity is quantified and compared with a blank control consisting of cells that were treated

with sodium azide. Only cells that are viable and proliferating will take up the radioactive thymidine. Therefore, there is an inverse relationship between the update of radioactivity and sensitivity of the cells to the agent(s) of interest.

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. 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 one 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. 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. Cells must be grown in a monolayer rather than in a 3-dimensional matrix.

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

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.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer
Current NCCN (v.1.2020) guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer state that "Chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3)."

Gastric Cancer
The NCCN (v.2.2020) guidelines for the treatment of gastric cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

Breast Cancer
The NCCN (v.4.2020) guidelines for the treatment of breast cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

Melanoma
The NCCN (v.3.2020) guidelines for the treatment of cutaneous melanoma do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

Non-Small Cell Lung Cancer
The NCCN (v.6.2020) guidelines for the treatment of non-small cell lung cancer do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

Uterine Neoplasms
The NCCN (v.1.2020) guidelines for the treatment of uterine neoplasms do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

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

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
The ongoing trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03133273[a]	Study of the Therapeutic Response and survival of Patients with Metastatic Colorectal Cancer (Stage IV) and Treated According to the Guidelines of a Chemosensitivity Test, Oncogramme®‡	256	Jul 2022

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

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03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. New policy.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. No change to coverage.
03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. No change to coverage.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. "ChemoFx" and "CorrectChemo" added to the list of investigational chemosensitivity assays; policy statements otherwise unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. No change to coverage.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. CorrectChemo assay removed from policy.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/21/2021	Coding update

Next Scheduled Review Date: 05/2022

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0564T, 81535, 81536, 87230, 88104 Add code eff 7/1/21: 0248U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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