MEDICAL POLICY – 2.03.01
In Vitro Chemoresistance and Chemosensitivity Assays

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Chemotherapy is the use of drugs to try to kill cancer cells. Assays (laboratory tests) have been created to try to find out if a person’s cancer might respond to or will resist specific chemotherapy drugs. Cells removed from the tumor during surgery or a biopsy are tested in a lab to see if they react to different chemotherapy drugs. High quality research studies don’t yet show whether these tests improve treatment results. For this reason chemoresistance and chemosensitivity lab tests are considered unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Assay</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>In vitro chemosensitivity assays</td>
<td>In vitro chemosensitivity assays are considered investigational, including, but not limited to:</td>
</tr>
<tr>
<td>Assay</td>
<td>Investigational</td>
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<tr>
<td></td>
<td>• The Histoculture Drug Response Assay</td>
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<td></td>
<td>• A fluorescent cytoprint assay</td>
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<tr>
<td></td>
<td>• The ChemoFx assay</td>
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</tbody>
</table>

**In vitro chemoresistance assays**

*In vitro chemoresistance assays are considered investigational, including, but not limited to:*

• Extreme Drug Resistance assays

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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**CPT**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0564T</td>
<td>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 (new code effective 1/1/20)</td>
</tr>
<tr>
<td>81535</td>
<td>Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stand and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination (applies to ChemoFX®)</td>
</tr>
<tr>
<td>81536</td>
<td>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)) (applies to ChemoFX®)</td>
</tr>
</tbody>
</table>

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## Related Information

N/A
Description

In vitro chemoresistance and chemosensitivity assays have been developed to provide information about the characteristics of an individual patient's malignancy to predict potential responsiveness of their cancer to specific drugs. Oncologists may sometimes use these assays to select treatment regimens for a patient. Several assays have been developed that differ concerning the processing of 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.

Background

A variety of chemoresistance and chemosensitivity assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and nonviable cells to quantify cell kill following exposure to a drug of interest. With few exceptions, drug doses used in the assays vary highly depending on tumor type and drug class, but all assays require drug exposures ranging from several-fold below physiologic relevance to several-fold above physiologic relevance. Although a variety of assays examine chemoresistance or chemosensitivity, only a few are commercially available. 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 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 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 differentiates 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 end point 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.\(^5\)

**Extreme Drug Resistance Assay**

The Oncotech Extreme Drug Resistance EDR\(^\circledR\) 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 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\(^\circledR\) (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 relation 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 adenosine triphosphate (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 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.

**Summary of Evidence**

For individuals who have cancer who are initiating chemotherapy who receive chemoresistance assays, the evidence includes correlational observational studies. Relevant outcomes are overall survival, 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 overall survival 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 an RCT, non-randomized studies, and correlational observational studies. The relevant outcomes are overall survival, 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 with standard care, including a RCT. 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 overall survival 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 overall survival are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Ongoing and Unpublished Clinical Trials

Some ongoing trials that might influence this policy are listed in **Table 1**.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT02580253</td>
<td>Adjuvant Chemotherapy Based on the Adenosine Triphosphate Tumor Chemosensitivity Assay for Hepatocellular Carcinoma After Liver Transplantation</td>
<td>300</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT03133273a</td>
<td>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®</td>
<td>230</td>
<td>Jul 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.

### Practice Guidelines and Position Statements

**National Comprehensive Cancer Network**

**Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer**

Current National Comprehensive Cancer Network (NCCN; v.1.2019) 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)”54
**Gastric Cancer**

The NCCN (v.2.2019) 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.1.2019) 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.2.2019) 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.4.2019) 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.3.2019) 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 use of chemotherapy sensitivity and resistance assays unless in a clinical trial setting.
Medicare National Coverage

There is no national coverage determination.

Regulatory Status

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

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/17/99</td>
<td>Replace Policy - Updated; policy unchanged.</td>
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<td>09/21/00</td>
<td>Replace Policy - Policy updated with reference to TEC Assessment; policy statement unchanged.</td>
</tr>
<tr>
<td>03/11/03</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged; 2002 updates and references added.</td>
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<tr>
<td>01/01/04</td>
<td>Replace Policy - CPT code updates only.</td>
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<td>05/11/04</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged, updated references provided.</td>
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<td>01/11/05</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged; references added.</td>
</tr>
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<td>11/11/05</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged; references updated.</td>
</tr>
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<td>06/23/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
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<td>10/10/06</td>
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<td>12/11/07</td>
<td>Delete Policy - No longer reviewed; policy deleted.</td>
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<td>12/14/10</td>
<td>Re-instate Policy - The policy has been reinstated to facilitate current request and support non-payment; additional code added 89240.</td>
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<td>07/12/11</td>
<td>Replace Policy - Policy updated with literature search. References 18, 30, 33, and 36 added. No change to policy statements. ICD-10 codes added to policy.</td>
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<td>05/22/12</td>
<td>Replace policy. Policy updated with literature search. No new references added. Policy statements unchanged.</td>
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<td>09/17/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<tr>
<td>07/26/13</td>
<td>Replace policy. Policy updated with literature search through March 2013. References 2, 3, 21, and 40 added. No change to policy statements.</td>
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<tr>
<td>06/19/14</td>
<td>Annual Review. Background and rationale sections reorganized. Policy updated with literature review through March 6, 2014. References 6-8, 40-42, 45, 47, 48 added; others renumbered/removed. Policy statements unchanged.</td>
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<tr>
<td>07/14/15</td>
<td>Archive Policy. This is old technology which has been replaced by genetic testing. There are few requests.</td>
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<tr>
<td>11/10/15</td>
<td>Re-instituting this policy due to more utilization and high cost of the test. Policy updated with literature review through March 12, 2015. References 4, 41-42, and 50 added. “ChemoFx” and “CorrectChemo” added to the list of investigational chemosensitivity assays; policy statements otherwise unchanged.</td>
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<td>01/19/16</td>
<td>Coding update. New CPT codes 81535 and 81536, effective 01/01/16, added to policy.</td>
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<tr>
<td>11/01/17</td>
<td>Annual Review, approved October 19, 2017. Policy updated with literature search</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td></td>
<td>through June 20, 2017; reference 35 and 49 added. Policy statements unchanged.</td>
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<tr>
<td>01/01/20</td>
<td>Coding updated, added CPT code 0564T (new code effective 1/1/20).</td>
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</tbody>
</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
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Español (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda en los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).


ไทย (Thai): ประกาศนี้มีสาระสำคัญ ประกาศนี้มีสาระสำคัญเกี่ยวกับการขอข้อมูลหรือการขอสิทธิของคุณกับ Premera Blue Cross และบริการที่เกี่ยวข้องในประเทศไทย คุณควรตรวจสอบด้วยว่าสามารถใช้ได้ในกรณีที่เกี่ยวข้องและมีการขอข้อมูลที่เกี่ยวข้องในประเทศไทยได้หรือไม่ โปรดติดต่อ 800-722-1471 (TTY: 800-842-5357).


Русский (Russian): Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian): Це повідомлення містить важливу інформацію. Ця повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).