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>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro chemosensitivity assays</td>
<td>In vitro chemosensitivity assays are considered investigational, including, but not limited to:</td>
</tr>
</tbody>
</table>
Assay

Investigational

- The Histoculture Drug Response Assay
- A fluorescent cytoprint assay
- The ChemoFx assay

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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<tbody>
<tr>
<td>CPT</td>
<td></td>
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<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>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review
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.
Extreme Drug Resistance Assay

The Oncotech Extreme Drug Resistance EDR® 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 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. 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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</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></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>256</td>
<td>Jul 2022</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.1.2020) 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)”54

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.55
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.56

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.57

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.58

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.59

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.60

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>
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<td>Update Scope and Disclaimer - No other changes.</td>
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<tr>
<td>10/10/06</td>
<td>Replace Policy - Policy reviewed with reference added; policy statement unchanged.</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>
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<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 otherwise 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. &quot;ChemoFx&quot; 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 01/01/2016, added to policy.</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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<tr>
<td>10/01/20</td>
<td>Annual Review, approved September 1, 2020. Policy updated with literature review through April, 2020; no references added. Policy statements unchanged. Removed CPT code 0564T.</td>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The
Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review
and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit
booklet or contact a member service representative to determine coverage for a specific medical service or supply.
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Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when
determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to
the limits and conditions of the member benefit plan. Members and their providers should consult the member
benefit booklet or contact a customer service representative to determine whether there are any benefit limitations
applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and discrimination on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, DC. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Email AppealsDepartmentInquiries@Premera.com

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action because of race, color, national origin, age, disability or sex.

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

Oromo (Ouromoo - Oromia [Amharic]):
Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti wu xawmooyaa bayyaa. Premera Blue Cross xawmooyaa kêu xwad abbaan nga adda rumbeng adda xamayyaa.

Arabic (العربية):

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或核保的重要訊息。本通知內容可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring higit sa paunawa ay maaaring naglalaman ng mahalagang impormasyon.

Román (Romanian):

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 указаны 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).

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 con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Póngase en contacto con nosotros al 800-722-1471 (TTY: 800-842-5357).


Român (Romanian):

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 указаны 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).

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