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</td>
</tr>
<tr>
<td></td>
<td>investigational, including, but not limited to:</td>
</tr>
</tbody>
</table>
### Assay

**Investigational**

- The Histoculture Drug Response Assay
- A fluorescent cytoprint assay
- The ChemoFx assay
- The CorrectChemo 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>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td></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>
<tr>
<td>89240</td>
<td>Unlisted miscellaneous pathology test</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 whether an individual patient’s cancer will respond to specific chemotherapy drugs. These assays are sometimes used by oncologists to select treatment regimens for a patient. Several assays have been developed that differ in how they process biologic samples and their specific 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 chemosensitivity and chemoresistance assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and nonviable cells to quantify how many cells were 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.

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 do not consistently demonstrate that chemoresistance assay results are associated with survival. Furthermore, no studies were identified that compared outcomes for patients managed with assay-directed therapy to those managed with 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 a randomized controlled trial (RCT), non-randomized studies, and correlational observational studies. 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, 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 better outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Nov 2018</td>
</tr>
<tr>
<td>NCT03133273*</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.

* Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (v.1.2017) state that “Chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy. (category 3)”\(^{54}\)

NCCN guidelines for the treatment of gastric cancer (v.2.2017)\(^{55}\) and uterine neoplasms (v.3.2017)\(^{56}\) do not discuss the use of chemoresistance or chemosensitivity assays as part of cancer management.

American Society of Clinical Oncology

The updated 2011 American Society of Clinical Oncology 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.\(^{57}\)

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Chemoresistance and chemosensitivity assays discussed in this policy are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/05/97</td>
<td>Add to Medicine Section - New Policy.</td>
</tr>
<tr>
<td>08/17/99</td>
<td>Replace Policy - Updated; policy unchanged.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>01/01/04</td>
<td>Replace Policy - CPT code updates only.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged, updated references provided.</td>
</tr>
<tr>
<td>01/11/05</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged; references added.</td>
</tr>
<tr>
<td>11/11/05</td>
<td>Replace Policy - Policy reviewed; policy statement unchanged; references updated.</td>
</tr>
<tr>
<td>06/23/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
</tr>
<tr>
<td>10/10/06</td>
<td>Replace Policy - Policy reviewed with reference added; policy statement unchanged.</td>
</tr>
<tr>
<td>12/11/07</td>
<td>Delete Policy - No longer reviewed; policy deleted.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>05/22/12</td>
<td>Replace policy. Policy updated with literature search. No new references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/17/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<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>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New CPT codes 81535 and 81536, effective 01/01/16, added to policy.</td>
</tr>
</tbody>
</table>

**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. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**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.
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- Provides free aids and services to people with disabilities to communicate effectively with, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  - Qualified interpreters
  - Information written in other languages

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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 with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. 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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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 by certain deadlines to keep your health coverage or help with costs. You may need to take action by certain deadlines to keep your health coverage or help with costs. You may need to take action by certain deadlines to keep your health coverage or help with costs. You may need to take action by certain deadlines to keep your health coverage or help with costs.

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

Arabic (Arabic):

العربية

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Român (Romanian):

Russian (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 необходимо 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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Polski (Polish):

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):