

05-86000-11

Original Effective Date: 12/15/02

Reviewed: 04/23/26

Revised: 05/15/26

Subject: In Vitro Chemoresistance and Chemosensitivity Assays

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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|------------------------------------|--------------------------------|-------------------------------|------------------------------------|-----------------------------|------------------------------------|
| Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions | Related Guidelines |
| Other | References | Updates | | | |

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. 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 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.

Summary and Analysis of Evidence: An UpToDate review on "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer" (Herzog, et al. 2026) includes "In vitro assays of chemosensitivity or resistance, such as the Chemo-FX assay or the extreme drug resistance (EDR) assay, are laboratory tests that have been developed as a method to select the optimal chemotherapy regimen (sensitivity assays) or identify those agents least likely to be effective (resistance assays). However, the utility of these assays has not been prospectively validated, and cost benefits have not been clearly demonstrated. We agree with the American Society of Clinical Oncology that concluded that the evidence is insufficient to justify the routine use of any of these assays outside of the clinical trial setting and that oncologists should make chemotherapy treatment recommendations on the basis of published clinical trial reports while taking into account an individual patient's treatment preferences." The National Comprehensive Cancer Network (NCCN) guideline "Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer" (V.1.2025) states "Chemosensitivity/resistance and/or other biomarker assays have been proposed for informing decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available, but the current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3)." It also includes "The NCCN Panel feels that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3), owing to the lack of demonstrable efficacy

for such an approach. ASCO also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.” The current published evidence is insufficient to determine the effects of the technology on health outcomes.

POSITION STATEMENT:

In vitro chemosensitivity assays are considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

In vitro chemoresistance assays are considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

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| 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 (Investigational) [ChemoFX®] |
| 81536 | 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, each additional single drug or drug combination (List separately in addition to code for primary procedure) (Investigational) [ChemoFX] |
| 0083U | Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug combinations (Investigational) [Onco4D™] |
| 0248U | Oncology, spheroid cell culture in 3D microenvironment, 12 drug panel, brain or brain metastasis response prediction for each drug (Investigational) [3D Predict™ Glioma] |
| 0249U | Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report (Investigational) [Theralink®] |
| 0435U | Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported based on cytotoxicity percentage observed, minimum of 14 drugs or drug combinations (Investigational) [ChemID®] |
| 0511U | Oncology (solid tumor), tumor cell culture in 3D microenvironment, 36 or more drug panel, reported as tumor-response prediction for each drug (Investigational) [PARIS®] |
| 0525U | Oncology, spheroid cell culture, 11-drug panel (carboplatin, docetaxel, doxorubicin, etoposide, gemcitabine, niraparib, olaparib, paclitaxel, rucaparib, topotecan, veliparib) ovarian, fallopian, or peritoneal response prediction for each drug (Investigational) [3D Predict™] |

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Human Tumor Stem Cell Drug Sensitivity Assays (190.7) located at [cms.gov](https://www.cms.gov).

The following is located at fcso.com: Local Coverage Article Billing and Coding: Molecular Pathology and Genetic Testing A58918.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#)

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

None applicable.

OTHER:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available.

Examples of in vitro chemosensitivity and in vitro chemoresistance assays:

3D Predict Glioma
Adenosine Triphosphate Bioluminescence
ChemoFX®
Clonogenic Cytotoxic Drug Resistance
CorrectChemo
Cytoprint
Differential Staining Cytotoxicity
EVA/PCD
Extreme Drug Resistance (EDR)
Fluorescent Cytoprint Assay (FCA)
Fluorometric Microculture Cytotoxicity
Histoculture Drug Response Assay (HDRA)
Microculture Kinetics (MICK)
Nonclonogenic Clonogenic Cytotoxic Drug Resistance
Onco4D™
Theralink®
Tritiated Thymine
Tumor Stem Cell Assay.

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3. Blue Cross Blue Shield Association TEC Assessment "Chemotherapy Sensitivity and Resistance Assays" (11/00), Tab 11.
4. Blue Cross Blue Shield Association TEC Assessment "Nonclonogenic Cytotoxic Drug Resistance Assay" (10/95), Tab 22.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Medical Policy and Coverage Committee on 04/23/26.

GUIDELINE UPDATE INFORMATION:

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| 12/15/02 | Reformat, review & revision of original Medical Coverage Guideline (09/94). |
| 06/15/03 | Revised billing/coding information section; deleted CPT codes: 87230, 88-104, 305, 313, 358, and 89050. |
| 06/15/04 | Scheduled review, no revisions. |

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| 03/15/05 | Scheduled review, no change in coverage statement. Revised description section. Format change, reimbursement information section. |
| 03/15/06 | Annual review; investigational status maintained. |
| 03/15/07 | Scheduled review; no change in coverage statement; references and Internet links updated. |
| 06/15/07 | Reformatted guideline. |
| 03/15/08 | Annual review: position statement maintained, description section updated, references updated. |
| 03/15/09 | Annual review: position statement maintained and references updated. |
| 03/15/10 | Annual review: position statement maintained; description section and references updated. |
| 02/15/11 | Annual review: position statement maintained and references updated. |
| 09/15/12 | Annual review; position statement maintained and references updated. |
| 02/15/13 | Revision; position statement, title, description section, and references updated. |
| 08/15/13 | Annual review; position statement maintained, program exception and references updates. |
| 06/15/14 | Annual review; position statement maintained and references updated. |
| 06/15/15 | Annual review; position statement maintained and references updated. |
| 01/01/16 | Annual HCPCS/CPT update; codes 81535 and 81536 added. |
| 11/15/16 | Revision; description, position statement, and references updated. |
| 10/15/18 | Review; investigational status maintained; position statements and references updated. |
| 01/01/20 | Annual CPT/HCPCS coding update. Added code 0564T. |
| 09/15/20 | Review; position statements maintained and references updated. |
| 11/15/21 | Review: Position statements maintained; references updated. |
| 07/01/23 | Review: Position statements, title, coding, and references updated. |
| 01/01/24 | Program exception and references updated. |
| 06/15/24 | Review: Position statements maintained; description and references updated. |
| 10/01/24 | Quarterly CPT/HCPCS coding update. Code 0248U revised. |
| 01/01/25 | Annual CPT/HCPCS coding update. Code 0564T deleted. |
| 06/15/25 | Review: Position statements maintained; description and coding updated. |
| 05/15/26 | Annual review: Position statements maintained; references updated. |