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Reviewed: 05/23/24

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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.

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. 2023) 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.1.2024) 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:

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 (brain), spheroid cell culture in a 3D microenvironment, 12 drug panel, tumor-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]
0564T	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 (**Investigational**)

Unlisted CPT codes 86849, 87999, 89240 may be used to report other chemoresistance and chemosensitivity assays.

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.

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

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.

REFERENCES:

1. Aoishi Y, Yoshimasu T, et al. Quantitative Evaluation of Hormesis in Breast Cancer Using Histoculture Drug Response Assay. Dose Response. 2019 Dec 26;17(4):1559325819896183.
2. Blue Cross Blue Shield Association TEC Assessment “Chemotherapy Sensitivity and Resistance Assays” (10/02), Tab 12.
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.
5. Burstein HJ, et al, American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Chemotherapy Sensitivity and Resistance Assays, J Clin Oncol. 2011 Aug 20;29(24):3328-30.
6. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Human Tumor Stem Cell Drug Sensitivity Assays (190.7); accessed at cms.gov.
7. Coleman RL Sabbatini P. Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease. In: UpToDate, Goff B, Dizon DS, Vora SR (Eds), UpToDate, Waltham, MA; accessed at uptodate.com.
8. Cree IA, Kurbacher CM, Lamont A, et al, A Prospective Randomized Controlled Trial of Tumour Chemosensitivity Assay Directed Chemotherapy Versus Physician’s Choice in Patients with Recurrent Platinum-resistant Ovarian Cancer, Anticancer Drugs, 2007 Oct; 18(9): 1093-101.
9. First Coast Service Options, Inc. (FCSO). Local Coverage Article Billing and Coding: Molecular Pathology and Genetic Testing A58918; accessed at fcso.com.
10. Herzog TJ, Armstrong DK. First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer, 2023. In: UpToDate. Goff B, Dizon DS, Vora SR (Eds), UpToDate, Waltham, MA; accessed April 2024 at uptodate.com.
11. Howard CM, Valluri J, Alberico A, et al. Analysis of Chemopredictive Assay for Targeting Cancer Stem Cells in Glioblastoma Patients. Transl Oncol. 2017 Apr;10(2):241-254.
12. Jun E, Park Y, et al. The identification of candidate effective combination regimens for pancreatic cancer using the histoculture drug response assay. Sci Rep. 2020 Jul 20;10(1):12004.
13. Kwon HY, Kim IK, et al. In Vitro Adenosine Triphosphate-Based Chemotherapy Response Assay as a Predictor of Clinical Response to Fluorouracil-Based Adjuvant Chemotherapy in Stage II Colorectal Cancer. Cancer Res Treat. 2016 Jul;48(3):970-7.
14. Jamal BT, Grillone GA, Jalisi S, Chemoresponse Assay in Head and Neck Cancer Patients: A Three-Year Follow Up. J Clin Diagn Res. 2017 May;11(5):XC01-XC03.
15. Kischkel FC, Meyer C, Eich J, et al, Prediction of clinical response to drugs in ovarian cancer using the chemotherapy resistance test (CTR-test). J Ovarian Res. 2017 Oct 27;10(1):72.
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology; accessed at nccn.org.
17. Shuford S, Lipinski L, et al. Prospective prediction of clinical drug response in high-grade gliomas using an ex vivo 3D cell culture assay. Neurooncol Adv. 2021 May 7;3(1):vdab065. Doi: 10.1093/noajnl/vdab065.
18. Sorlie T, Perou CM, Fan C, et al, Gene Expression Profiles Do Not Consistently Predict the Clinical Treatment Response in Locally Advanced Breast Cancer, Mol Cancer Ther. 2006 Nov; 5(11): 2914-8.

19. Suksawat M, Klanrit P, et al. In Vitro and Molecular Chemosensitivity in Human Cholangiocarcinoma Tissues. PloS One. 2019 Sep 10;14(9):e0222140.
20. Tanigawa N, Yamaue H, Ohyama S, et al. Exploratory phase II trial in a multicenter setting to evaluate the clinical value of a chemosensitivity test in patients with gastric cancer (JACCRO-GC 04, Kubota memorial trial). Gastric Cancer. Apr 2016;19(2):350-360.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Medical Policy and Coverage Committee on 05/23/24.

GUIDELINE UPDATE INFORMATION:

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.
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.