Anthem

Medical Policy

Subject: In Vitro Chemosensitivity Assays and In Vitro Chemoresistance Assays
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Description/Scope

This document addresses in vitro chemosensitivity assays and in vitro chemoresistance assays which have been proposed as a means of predicting the in vivo tumor response to various chemotherapies. Several assays have been developed that differ in their processing and in the technique used to measure drug sensitivity. However, they typically involve isolation of tumor cells from biopsy specimens, incubation of the cells with drugs and assessment of cell survival. Results may be reported as drug sensitive, drug resistant or intermediate. Drugs identified as drug sensitive are thought to be a potentially effective in vivo chemotherapy.

Position Statement

Not Medically Necessary:

In vitro chemosensitivity assays, as a guide to selection of chemotherapeutic drugs for individuals with cancer, are considered**not medically necessary** for all indications.

In vitro chemoresistance assays including, but not limited to, extreme drug resistance assays are considered**not medically necessary** for all indications.

Rationale

A number of studies have evaluated the correlation between in vitro chemosensitivity assays and response to chemotherapy, but to date, the evidence is insufficient to conclude that in vitro chemosensitivity or chemoresistance testing leads to improved health management or outcomes. In a 2017 meta-analysis Blom and colleagues summarized findings of 34 studies on a variety of tests and indications. They evaluated the association between in vitro testing and clinical response (complete or partial remission). Using 70 correlations derived from assay-guided treatment, the predictive value of ex vivo testing had a pooled sensitivity of 92% (95% confidence interval [CI], 79-98%) and a pooled specificity of 53% (95% CI, 35-71%). A limitation of the analysis is that most of the studies were retrospective and findings were not used to guide treatment.

Among the prospective studies was one published by Kim and colleagues in 2010. This study attempted to determine the most accurate analytic method to define in vitro chemosensitivity and to assess the accuracy of ATP-based chemotherapy response assay (ATP-CRA). A total of 48 individuals with chemo-naïve, histologically confirmed, locally advanced or metastatic gastric cancer were enrolled in this study and treated with combination chemotherapy of paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 for a maximum of six cycles after obtaining specimens for ATP-CRA. Investigators performed the receiver operator characteristic curve analysis using individual responses by WHO criteria and obtained ATP-CRA results to define the method with the highest accuracy. Median progression-free survival (PFS) was 4.2 months (95% CI, 3.4-5.0) and median overall survival was 11.8 months (95% CI, 9.7-13.8) for all those enrolled. The chemosensitivity index method demonstrated highest accuracy of 77.8% by ROC curve analysis, and the specificity, sensitivity, positive and negative predictive values were 95.7%, 46.2%, 85.7%, and 75.9% respectively. The in vitro chemosensitive group showed a higher response rate (85.7% vs. 24.1%) (p=0.005) compared to the chemoresistant group. The authors concluded that ATP-CRA could predict clinical response to paclitaxel and cisplatin chemotherapy with high accuracy in individuals with advanced gastric cancer and results support the use of ATP-CRA in further validation studies and assay-guided clinical trials. However, there were numerous study limitations noted including, (1) the study took almost 3 years to enroll 36 subjects acceptable for evaluation; (2) many samples were not enrolled due to bacterial contamination and an inadequate amount of tissue; (3) the study was terminated early due to a very poor accrual of subjects, which resulted in an inadequate power to test the accuracy as originally planned; (4) study results needed validation by an independent cohort; and (5) the study may have been subject to bias because the clinical response was evaluated in participating centers by investigators who were blind to the in vitro chemosensitivity results but there was no independent review of response evaluation.

Another prospective study, reported by Rutherford and colleagues in 2013, was designed to assess whether the ChemoFX® assay was predictive of outcomes among women with histologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Physicians were blinded to the assay results and treatment was selected based on the oncologist's medical judgment from1 of 15 prospectively specified protocols. A total of 262 (78.2% of total) had both available clinical follow-up data and a ChemoFX result. Cancer cells were classified based on the ChemoFX result as sensitive, intermediate, or resistant to each of several chemotherapeutic agents. Those treated with an assay-sensitive regimen had a PFS median of 8.8 months, compared with 5.9 months for those with assay-intermediate or -resistant regimens (hazard ratio [HR], 0.67, p=0.009). Mean overall survival was 37.5 months for women treated with an assay-sensitive regimen, compared with 23.9 months for those with assay-intermediate or -resistant regimens (HR=0.67, p=0.010). Although study results showed potential promise, the selection of a chemotherapeutic agent was not based on assay results but on physician judgment and the impact on health outcomes cannot be determined.

Herzog and colleagues (2010) evaluated in vitro tumor responses to platinum therapy by performing chemosensitivity testing on tumors from 192 women with primary ovarian cancer. Tumors were categorized as responsive, intermediately responsive, and nonresponsive to chemotherapy. Median overall survival was 72.5 months for women with tumors classified as responsive, 48.6 months for intermediately responsive, and 28.2 months for nonresponsive (p=0.03; HR=0.70; 95% CI, 0.50-0.97). The authors concluded that the prediction of response to platinum agents by the chemosensitivity testing was consistent with expected population response rates. Limitations of this series included restriction of the survival analysis to only platinum agents in the primary setting, lack of information on subsequent chemotherapy, death was used as the primary endpoint of the study, and no assessments of clinical tumor response or disease status at death were available.

A prospective study by Howard and colleagues (2017), which used the ChemoID test, assessed health outcomes but did not use the test results to guide treatment. A total of 41 individuals with glioblastoma (GBM) underwent standard-of-care treatment with temozolomide (TMZ)/radiotherapy and optimal surgical resection. Surgical biopsy samples were tested with ChemoID. The primary endpoint of the study was 12-month response to TMZ therapy, defined as lack of tumor recurrence. Tumor recurrence was significantly associated with ChemoID assay results. That is, for every 5% increase in TMZ cancer stem cell percent kill as identified

by the test, there was a two-fold increase in 12-month nonrecurrence of cancer (odds ratio [OR]=2.2; 95% CI, 1.16-4.17; p=0.016). This cohort study was intended as a preliminary study to inform design of a randomized controlled trial (RCT). An RCT would provide data on whether individuals prospectively managed with the ChemoID test would have improved outcomes.

Several non-randomized studies used the microculture kinetic (MiCK) assay (Ballard 2010; Kravtsov, 1998; Liminga, 2000; Salom 2012; Strickland, 2013). The MiCK assay has been purported to indicate which type of chemotherapy may be most effective against the tumor cells of a particular individual; however, current published evidence is insufficient to demonstrate its clinical utility.

Salom and colleagues (2012) performed a prospective, non-randomized multi-institutional trial to determine if the MiCK assay could predict the best therapy for ovarian cancer. Specimens were submitted from 210 subjects between May, 2006 and September, 2010. A total of 60 specimens could not be used due to an insufficient number of viable cancer cells (40% of the 60), spontaneous necrosis in transit (17%), or transit delays. The remaining 150 subjects had tumors analyzed for patterns of in vitro assay of drug effects on ovarian cancer cells. The assay was performed prior to initiation of chemotherapy; however, results were not provided to the treating physicians and treatment was selected based on clinical criteria. Individual outcomes were compared to the drug-induced apoptosis observed in the assay. Overall survival in primary therapy, chemotherapy naïve participants with Stage III or IV disease was longer if an individual received a chemotherapy which was best in the MiCK assay, compared to shorter survival in those who received a chemotherapy that was not the best. Standard therapy with carboplatin plus paclitaxel (C + P) was not the best chemotherapy in the MiCK assay in 44% of subjects studied. If an individual received C + P and it was the best chemotherapy in the MiCK assay, their survival was longer than those receiving C + P when it was not the best chemotherapy in the assay. Relapse-free interval for those receiving primary therapy was longer if the best chemotherapy from the MiCK assay was received. Response rates (CR + PR) were higher if physicians used an active chemotherapy based on the MiCK assay. The authors stated that this study justifies an RCT, and quantifies the benefits in outcomes on which a randomized study can be developed (for power determinations and study size requirements).

In 2010, Ballard and colleagues studied the MiCK assay in endometrial cancer specimens. Endometrial cancer specimens from total abdominal hysterectomies were processed at a central laboratory. Single and combination regimens were tested: combinations of doxorubicin, cisplatin, and paclitaxel and carboplatin and paclitaxel (Gynecologic Oncology Group [GOG] 209 endometrial cancer phase III trial arms) as well as single agent testing with paclitaxel, carboplatin, doxorubicin, cisplatin, ifosfamide, and vincristine (active agents in GOG trials). Apoptosis was measured continuously over 48 hours. Fifteen of 19 individuals were reported to have had successful assays. The highest mean chemosensitivity was noted in the combination of cisplatin, doxorubicin, and paclitaxel with lower mean chemosensitivity for carboplatin and paclitaxel. Combination chemotherapy had higher chemosensitivity than single drug chemotherapy. However, in 25% of subjects a single drug had higher chemosensitivity than combination chemotherapy. As single agents, ifosfamide, cisplatin, and paclitaxel had the highest kinetic unit values. The authors concluded that MiCK may be useful in future new drug testing and individualizing the chemotherapy management of endometrial cancer. Limitations of this study included a small sample size.

There is one published RCT comparing individuals managed with and without in vitro chemosensitivity or chemoresistance assays. This study, published by Cree and colleagues in 2007, studied tumor chemosensitivity assay-directed chemotherapy versus physician's choice in recurrent platinum-resistant ovarian cancer. The primary aim of this trial was to determine response rate and progression-free survival following chemotherapy in individuals with platinum-resistant recurrent ovarian cancer who had received treatment according to an adenosine triphosphate (ATP) based tumor chemosensitivity assay in comparison with physician's choice. A total of 180 subjects were randomized into two groups with median ages of 59 and 61 years. Ninety-four individuals received assay-directed chemotherapy and 86 received physician's choice therapy. The two primary end points studied were response rate and progression-free survival. Response could only be assessed in 147 subjects, and 40.5% achieved a partial or complete response in the assay-directed group versus a 31.5% response in the physician's choice group ($p<0.3$; not significant). In an intention-to-treat analysis, response rates were 31% in the assay-directed group vs. 26% in the physician choice group. Intention-to-treat analysis showed a median progression-free survival of 93 days in the physician's choice group and 104 days in the assay-directed group (HR=0.8; not significant). No difference was seen in overall survival between the two groups. The authors concluded the ATP-based tumor chemosensitivity assay remains an investigational method in this condition.

In 2021, Shuford and colleagues evaluated the 3D-Predict's ability to predict drug response in 33 prospectively enrolled adults (≥ 18 years) with suspected or known high-grade glioma who received standard of care treatment; both enrollees and their practitioners were blinded to the assay results. The predicted 'responders' had a median overall survival of 11.6 months (4.2-30.4) compared to 5.9 months (3.3-11.7) for predicted 'nonresponders' (HR=0.35; 95% CI, 0.13 to 0.90; p=0.04). Given the limited sample size, marginal significance and lack of demonstrated clinical utility beyond case series, further study is warranted.

The American Society of Clinical Oncology (ASCO) (2011) does not recommend the use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individuals outside of the clinical trial setting. ASCO cited an insufficient evidence base to support the use in oncology practice. ASCO indicates that a review of the literature did not identify any chemotherapy sensitivity and resistance assays for which the evidence was sufficient to support the use in oncology practice.

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guideline for ovarian cancer (V1.2022) indicates that the current level of evidence for chemosensitivity/resistance assays is not sufficient to supplant generally accepted standards of chemotherapy (category 3). A category 3 recommendation reflects major disagreement amongst a multidisciplinary panel of oncology experts.

Evidence from available studies is insufficient to conclude that in vitro chemosensitivity or chemoresistance testing leads to improved health management or outcomes. Only one RCT has compared a testing-dependent and testing-independent approach to disease management and this study did not find significantly improved outcomes when chemotherapy selection was based on the results of in vitro chemosensitivity testing compared with physician choice. Neither major professional oncology group (American Society of Clinical Oncology and National Comprehensive Cancer Network) recommend the use of these assays outside a clinical trial.

Background/Overview

Chemotherapy sensitivity and resistance assays may also be called human tumor stem cell drug sensitivity assays, nonclonogenic or clonogenic cytotoxic drug resistance assays, tumor stem cell assays, or differential staining cytotoxic assays. These assays are intended to provide oncologists with information which assists in the selection of chemotherapy drugs, to select potentially more effective chemotherapy regimens and to avoid the toxicity of potentially ineffective chemotherapy drugs for an individual.

In vitro chemosensitivity assays are proposed to screen potential anticancer drugs, predict the effect of these drugs on tumors and determine the most appropriate chemotherapeutic regimen. The process assumes that the drugs most effective for treating a particular cancer can be identified. Therefore, in vitro chemosensitivity assays involve tumor cells obtained from an individual which are cultured and exposed to specific drugs in the laboratory setting. This process is done over a set period to evaluate survival and resistance of tumor cells to selected drugs. The ineffective drugs, where extreme resistance is exhibited, are eliminated. Examples

of in vitro chemosensitivity assays include but are not limited to:

- Histoculture Drug Response Assay
- Afluorescent cytoprint assay
- ChemoFX assay
- CorrectChemo assay (previously known as the Microculture Kinetic [MiCK)] assay)

In vitro chemoresistance assays are reported to provide similar information as in vitro chemosensitivity assays. In addition, they also are said to deselect those drugs that are of no benefit. One of the most widely used techniques is the Extreme Drug Resistance assay (EDR®). In this assay, cultured cells are exposed to high concentrations of selected chemotherapeutic agents for prolonged periods, far exceeding the exposure anticipated in vivo. Cell lines that survive this exposure are characterized as showing extreme drug resistance. These drugs are then considered potentially ineffective and a physician may be prompted to select another chemotherapeutic agent.

Definitions

Apoptosis: The innate ability of a cell to undergo programmed death due to detrimental or incompatible derangements in its DNA.

Assay: A test to determine the make-up or potency of a drug.

Cytotoxic drug: Drugs that possess a destructive action on specific cells; often refers to drugs used to fight cancer, such as chemotherapy.

In vitro: Within a glass petri dish or test tube; in an artificial environment; outside of the body.

In vivo: Within the living body.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services are Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as not medically necessary.

CPT

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 ChemoFX®, Helomics, Corp
81536	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 ChemoFX®, Helomics, Corp
86849	Unlisted immunology procedure [when specified as in vitro chemosensitivity or in vitro chemoresistance assay, ex vivo analysis of programmed cell death]
87999	Unlisted microbiology procedure [when specified as in vitro chemosensitivity or in vitro chemoresistance assay]
89240	Unlisted miscellaneous pathology test [when specified as in vitro chemosensitivity or in vitro chemoresistance assay]
0248U	Oncology (brain), spheroid cell culture in a 3D microenvironment, 12 drug panel, tumor-response prediction for each drug 3D Predict Glioma, KIYATEC®, Inc
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 ChemoID®, ChemoID® Lab, Cordgenics, LLC
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

ICD-10 Diagnosis

	All diagnoses

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11. Shuford S, Lipinski L, Abad A, et al. Prospective prediction of clinical drug response in high-grade gliomas using an ex vivo 3D cell culture assay. Neurooncol Adv. 2021 ;3(1):vdab065.
12. Shuford S, Wilhelm C, Rayner M, et al. Prospective validation of an ex vivo, patient-derived 3D spheroid model for response predictions in newly diagnosed ovarian cancer. Sci Rep. 2019. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6671958/pdf/41598_2019_Article_47578.pdf. Accessed on July 11, 2023.
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Government Agency, Medical Society, and other Authoritative Publications:

1. Burstein HJ, Mangu PB, Somerfield MR, et al; American Society of Clinical Oncology (ASCO). American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. J Clin Oncol. 2011; 29(24):3328-3330.
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3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Ovarian Cancer (V.2.2023). Revised June 2, 2023. For additional information visit the NCCN website: http://www.nccn.org. Accessed on July 11, 2023.
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Index

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.

Document History

Status	Date	Action
	12/28/2023	Updated Coding section with 01/01/2024 CPT changes, added 0435U.
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section
	03/29/2023	Updated Coding section with 04/01/2023 CPT changes; removed deleted codes 0324U, 0325U.
Reviewed	08/11/2022	MPTAC review. Description/Scope, Rationale, Reference and Index sections updated.
	06/29/2022	Updated Coding section with 07/01/2022 CPT changes; added 0324U, 0325U.
Reviewed	08/12/2021	MPTAC review. Rationale and Reference sections updated. Updated Coding section; added 0248U.
Revised	02/11/2021	MPTAC review. Revised 'in all cases' to 'for all indications' in the INV/NMN statements. Rationale and Reference sections updated.
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	12/31/2019	Updated Coding section with 01/01/2020 CPT changes; added 0564T.
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Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. References section updated.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date". Description/Scope, Rationale and References sections updated.
Reviewed	05/04/2017	MPTAC review.

Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Rationale and References sections updated.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Rationale, Background, References and Index sections updated.
	01/01/2016	Updated Coding section with 01/01/2016 CPT changes; removed ICD-9 codes.
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Reviewed	05/17/2007	MPTAC review.
Reviewed	05/16/2007	Hematology/Oncology Subcommittee review. References and rationale updated.
Reviewed	06/08/2006	MPTAC review. Rationale and references updated.
Reviewed	06/07/2006	Hematology/Oncology Subcommittee review.
	11/18/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	04/28/2005	LAB.00003	In Vitro Chemotherapy Sensitivity and In Vitro Resistance Assays
WellPoint Health Networks, Inc.	12/02/2004	2.11.04	Human Tumor Cell In Vitro Chemosensitivity Assay
	12/02/2004	2.11.15	Human Tumor Cell In Vitro Chemoresistance Assay

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