

MEDICAL POLICY



SUBJECT: TUMOR CHEMORESISTANCE AND CHEMOSENSITIVITY ASSAYS	EFFECTIVE DATE: 06/21/07
POLICY NUMBER: 2.02.32	REVISED DATE: 06/19/08, 05/28/09, 05/27/10, 05/19/11, 05/24/12, 06/20/13, 07/17/14, 06/18/15, 06/16/16, 06/15/17, 06/21/18
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- *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*
- *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.*
- *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT:

- I. Based upon our criteria and review of the peer-reviewed literature, tumor *chemoresistance* assays including but not limited to extreme drug resistance assays, as a guide to selection of chemotherapeutic drugs for individuals with cancer, have not been medically proven to be effective and are considered **investigational**.
- II. Based upon our criteria and review of the peer-reviewed literature, tumor *chemosensitivity* assays including but not limited to the histoculture drug response assay and the fluorescent cytoprint assay, as a guide to selection of chemotherapeutic drugs for individuals with cancer, have not been medically proven to be effective and are considered **investigational**.

POLICY GUIDELINES:

- I. Chemotherapy sensitivity and resistance assays are specialized laboratory tests typically performed in reference laboratories.
- II. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

Tumor chemoresistance and chemosensitivity assays have been investigated as a means of predicting tumor response to various chemotherapies. Tumor *chemoresistance* assays are focused on identifying resistant drugs. Tumor *chemosensitivity* assays are intended to predict the sensitivity of various tumors to chemotherapeutic agents. These assays have been proposed for use by oncologists to select chemotherapy regimens for individual patients. A variety of assays have been developed that differ in their processing and in the technique used to measure sensitivity or resistance. However, all involve the same four basic steps: 1) isolation of cells, 2) incubation of cells with drugs, 3) assessment of cell survival, and 4) interpretation of the result. A variety of techniques have been evaluated to assess cell survival, including the DISC (differential staining cytotoxicity) assay, the thymidine incorporation assay, fluorescence (cytoprint) assays, and the MTT (methylthiazolyl-diphenyl-tetrazolium bromide) assay.

Results are reported as either drug sensitive, drug resistant, or intermediate. Drugs identified as *drug sensitive* are thought to be potentially effective in chemotherapy, while drugs identified as *resistant* are thought to be potentially ineffective chemotherapies. Chemoresistance assays are most commonly used and a technique has been refined into an assay that predicts extreme drug resistance (EDR®).

RATIONALE:

A 2002 BlueCross BlueShield technology assessment indicated that, based on available data within published peer-reviewed literature, there was insufficient evidence to determine whether assay-guided chemotherapy improves health outcomes.

In 2004, the American Society of Clinical Oncology (ASCO) published a technology assessment of chemotherapy sensitivity and resistance assays (CSRA) along with a systematic review of the literature. The assessment concluded that review of the literature did not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice. ASCO's current recommendation is that the use of CSRAs for individual patients is, "not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published

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reports of clinical trials and a patient’s health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.”

For epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, the National Comprehensive Cancer Network (2018) does not recommend chemosensitivity/resistance or other biomarker assays for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is insufficient to supplant standard-of-care chemotherapy (Category 3).

Available clinical evidence regarding these assays consists of case series and retrospective studies with small sample sizes and methodologic flaws. These results do not establish the relative effectiveness of assay-guided treatment and empiric treatment. Randomized trials are needed.

Chemoresistance Assays. Chemoresistance assays will depend on the prior probability of response to a given chemotherapy. Since they are used to deselect potential chemotherapies, the negative predictive value (NPV) is the key statistical measure. Or, the likelihood that chemoresistance as measured in vitro will correspond to a lack of clinical effect. Unless the NPV value is high, there is a chance that clinical decision-making based on a chemoresistance assay could inappropriately exclude an effective therapy. The NPV will vary according to the prior probability of chemoresistance. Chemoresistance assays have the highest clinical relevance in tumors with a low probability of response. However, it is still unclear how this information will affect clinical decision making and whether health outcomes are improved as a result.

The extreme drug resistance (EDR) was specifically designed to produce a very high negative predictive value (greater than 99%) such that the possibility of inappropriately excluding effective chemotherapy is remote in all clinical situations. Clinical data are still inadequate to determine whether the use of EDR assays to deselect ineffective chemotherapies result in improved health benefits. Avoidance of the toxicity of ineffective drugs is an intermediate outcome. Improved patient survival is the relevant outcome. The bulk of the literature regarding EDR assays have focused on correlation studies that correlate results from predictive in vitro assays with observed outcomes of chemotherapy. Correlations studies are inadequate because such studies often aggregate patients with different tumor types, disease characteristics, chemotherapy options, and probabilities of response. Therefore, the accuracy of each assay probably varies across different malignancies and patient characteristics. Also, the method by which assay results are translated into treatment decisions is not standardized. And it is important to consider not only response, but also survival and adverse effects. The overall value of assay-guided therapy depends on the net balance of all health outcomes observed after treatment for all patients subjected to testing, regardless of the assay results or the accuracy of its prediction for response. The use of chemoresistance or EDR assays has not been established as a standard of practice in the clinical setting.

Chemosensitivity Assays. Chemosensitivity assays, in general, have poor positive predictive values (PPV), the likelihood that drugs shown to be effective in vitro will produce a positive clinical response. A meta-analysis of 54 different retrospective studies reported a PPV of only 69%. Several prospective trials have reported technical challenges and inconclusive results. Results of a multicenter Phase II trial conducted to investigate the feasibility of using an in vitro chemosensitivity assay in a multicenter environment, the efficacy of an individualized assay-directed therapy program, and to prove a potential association between in vitro and in vivo therapy based on tumor response and survival in patients diagnosed with melanoma were published in 2006. Of 80 patients, 57 received assay directed therapy and the remainder received other therapy. Assay results showed drug combinations caused a higher sensitivity level than single agents, and in vitro sensitivity to dacarbazine was poor with nearly all samples showing resistance to this drug. There was a median overall survival of 8.8 months. Authors concluded that subsequent studies are necessary to optimize dosages, treatment regimens and specified patient selection criteria.

Trials are underway for testing chemosensitivity using a microplate adenosine triphosphate-based luminescence chemosensitivity assay (ATP-TCA). This nonclonogenic assay is said to be able to overcome limitations with older assays and therefore allow for testing of most tumor specimens.

Cree and colleagues (2008) reported on a prospective randomized trial of chemosensitivity assay-directed chemotherapy versus physician’s choice in patients with recurrent platinum-resistant ovarian cancer. The primary aim of this randomized trial was to determine response rate and progression-free survival following chemotherapy in patients who had been

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treated according to an ATP-based tumor chemosensitivity assay in comparison with physician's choice. A total of 180 patients were randomized to assay-directed therapy (n=94) or physician's-choice chemotherapy (n=86). Median follow-up at analysis was 18 months; response was assessable in 147 (82%) patients: 31.5% achieved a partial or complete response in the physician's-choice group compared with 40.5% in the assay-directed group (26% vs. 31% by intention-to-treat analysis, respectively). 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 (hazard ratio 0.8, not significant). No difference was seen in overall survival between the groups, although 12/39 (41%) of patients who crossed over from the physician's-choice arm obtained a response. Increased use of combination therapy was seen in the physician's-choice arm during the study as a result of the observed effects of assay-directed therapy in patients. The authors concluded that this small randomized, clinical trial documented a trend toward improved response and progression-free survival for assay-directed treatment and that chemosensitivity testing might provide useful information in some patients with ovarian cancer. They also noted that the ATP-based tumor chemosensitivity assay remains an investigational method in this condition.

The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (v.2.2018) states the following, "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)".

FDA Status. The FDA clears laboratory tests for marketing for in vitro diagnostic use. Under CLIA requirements, laboratories introducing a new test method that is 1) an FDA-cleared test that is categorized as high complexity; 2) an FDA-cleared moderate complexity test that has been modified by the laboratory; 3) a test established in-house; or 4) a test not subject to FDA clearance, must verify or establish performance specifications for accuracy, precision, analytical sensitivity, analytical specificity, reportable range, and reference range prior to reporting patient test results.

Chemotherapy sensitivity and resistance assays and the laboratories that perform them fall under the general regulations applicable to all clinical laboratories and laboratory tests. Performance of medical laboratory testing is regulated by CMS under provisions of the Guidance for Clinical Laboratory Improvement Amendments of 1988 (CLIA). Under provisions of these regulations, clinical laboratories must obtain a certificate for the complexity of testing being performed. The ChemoFx® Assay, Precision Therapeutics, Inc (Pittsburgh, PA) is a commercially available assay and measures chemosensitivity and resistance.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT: No specific codes

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HCPCS: No specific codes

ICD10: Investigational for all codes

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KEY WORDS:

Chemoresistance assay, Chemosensitivity assay, Cytoprint, EDR Assay, Extreme Drug Resistance Assay, Histoculture Drug Response Assay.

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CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for tumor chemoresistance and chemosensitivity assays.