



IN VITRO CHEMOSENSITIVITY AND CHEMORESISTANCE ASSAYS HS-061



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In Vitro Chemosensitivity and Chemoresistance Assays

Policy Number: HS-061

Original Effective Date: 11/20/2008

**Revised Date(s): 11/24/2009;
11/12/2010; 10/6/2011**

DISCLAIMER

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

BACKGROUND

In vitro assays are intended for use with clinical decision-making to guide the pretherapeutic selection of chemotherapeutic agents. It is presumed that drugs deemed most effective or least effective in vivo can be identified prospectively by how effective they are in an in vitro test. There are a variety of in vitro assays, but they share four basic steps: isolation of tumor cells, incubation of cells with drugs, assessment of cell survival, and interpretation of result. In vitro extreme drug resistance (EDR) assays differ from in vitro drug sensitivity assays. While drug sensitivity assays presumably help the physician select an active chemotherapy agent, EDR assays predict drugs for which the tumor is extremely resistant. Reportedly, EDR effectively eliminates from consideration drugs to which the patient has a less than 1% chance of benefiting if administered the drug. The identification of ineffective chemotherapeutic agents helps prevent unnecessary patient exposure to toxic agents and eliminates the cost of inactive chemotherapy.

There is a paucity of clinical studies that investigate the value of chemoresistance assays for the selection of chemotherapy. The peer-reviewed, published medical and scientific literature includes only one small (n=66) uncontrolled case series in which chemoresistance assay results were used to select patient treatment and survival was the primary trial end-point. The literature has significant methodological weaknesses, which make it inadequate for determining the efficacy of basing cancer chemotherapeutic treatment decisions on the results of in vitro chemoresistance assays. The major limitation in the literature is the absence of randomized controlled trials evaluating the survival rate of patients treated with assay-directed regimens compared with that of a control group treated with an empiric regimen. The preponderance of the evidence regarding chemoresistance assays is derived from correlational trials that do not use intent-to-treat analysis or investigate survival rates. Although correlational studies may provide interesting insights, they are not an adequate test of the hypothesis that pre-therapeutic decisions informed by in vitro EDR assay results affect better patient outcomes than decisions not so informed. Therefore, the results of these correlational trials have not been considered when determining the HAYES Rating for chemoresistance assays.

Although proponents of EDR assay testing contend that the benefits of chemoresistance testing can be demonstrated in mathematical models, critics contend that the only relevant outcome is improved patient outcome. In the clinical setting, the potential role of chemoresistance assays would vary according to the assay feasibility, tumor type, the role of chemotherapy, and the therapeutic agents tested. The prevailing peer-reviewed medical literature is inadequate for demonstrating the efficacy of these assays.

The available literature contained five prospective studies that met the criteria for detailed review and that evaluated in vitro chemosensitivity testing for small-cell lung cancer, non-small-cell lung cancer, or ovarian cancer. In these studies, patients were non-randomly assigned to either standard therapy or to chemotherapy based on in vitro chemosensitivity testing. Patients assigned to standard therapy were primarily those from whom tumor cells could not be cultured, which was the case for between 55% and 81% of patients. For the purposes of comparing results from patients who did and did not have chemotherapy guided by chemosensitivity testing, the outcome measures were response to therapy, either tumor or clinical response, and survival. These studies provided little evidence that patient outcomes improve when in vitro chemosensitivity testing guides the selection of chemotherapeutic agents. Two of the studies reported no improvement in tumor response for patients who were treated on the basis of in vitro chemosensitivity, compared with those who were treated with standard chemotherapeutic regimens. One study reported a trend toward improved tumor response that did not achieve statistical significance, while another study reported that chemotherapy guided by chemosensitivity testing provided a statistically significant increase in tumor response. Of the three studies that provided data on patient survival, only one study documented a positive effect of in vitro chemosensitivity testing on survival. In this study, part of a cohort of previously untreated patients in relatively early stages of small-cell lung cancer underwent secondary chemotherapy guided by chemosensitivity testing.

There is insufficient evidence from the available studies to conclude that in vitro chemosensitivity testing leads to improved patient management or health outcomes. Only one of the five available studies reported a survival benefit associated with chemotherapy based on in vitro chemosensitivity testing, when compared with chemotherapy based on standard regimens or clinical indicators. In addition, all of the studies reported that tumor cells could be successfully cultured in only a small percentage of patients (from Hayes, 2000 and 2003).

Due to the insufficient evidence regarding both assays, they are considered experimental and investigational and NOT a covered benefit.

Professional Statements

The National Cancer Institute (2003) stated that although scientists are investigating in vitro drug sensitivity testing for cancer therapy, the current evidence does not justify routine use of this research tool for patients. The NCI has concluded that, at present, this testing is too cumbersome and expensive, and it does not provide additional benefits compared with the knowledge and judgment of experienced clinicians.

The American Society of Clinical Oncology (2004) stated that “the use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published 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”.

A 2011 update to the American Society of Clinical Oncology clinical practice guideline maintains that evidence is insufficient to support use of CSRAs in oncology practice and not recommended outside of the clinical trial setting (Burstein, Mangu, Somerfield, Schrag, Samson, Holt, & et al, 2011). description and general information about the procedure, test, etc.

POSITION STATEMENT

In vitro chemosensitivity and in vitro chemoresistance assays **are considered experimental and investigational and are NOT a covered benefit.**

CODING

Non-covered CPT®* Code

88299† Unlisted cytogenetic study when billed for chemoresistance or chemosensitivity assays.
†Note: Experimental/Investigational/Unproven and not covered when used to report in vitro chemoresistance or chemosensitivity assays.

Non-covered ICD-9-CM Procedure Code Not applicable.

Non-covered HCPCS Codes No specific codes.

Non-Covered ICD-9-CM Diagnosis Codes All diagnoses are non-covered.

*Current Procedural Terminology (CPT®) ©2011 American Medical Association: Chicago, IL.

REFERENCES

Peer Reviewed

1. Burstein, H.J., Mangu, P.B., Somerfield, M.R., Schrag, D., Samson, D., Holt, L., & et al. (2011). American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. *Journal of Clinical Oncology*, 29(24), 3328-3330.
2. Hayes Directory. (2003, February 28). In vitro chemosensitivity assays in cancer treatment. Retrieved from <http://www.hayesince.com>
3. Hayes Directory. (2000, May 23). In vitro extreme drug resistance assays in cancer treatment. Retrieved from <http://www.hayesince.com>
4. Schrag, D., Garewal, H.S., Burstein, H.J., Samson, D.J., Von Hoff, D.D., & Somerfield, M.R. (2004). American Society of Clinical Oncology technology assessment: chemotherapy sensitivity and resistance assays. *Journal of Clinical Oncology*, 22(17), 3631-3638.

Government Agencies, Professional and Medical Organizations

1. Centers for Medicare and Medicaid Services. (1996, July 1). National coverage determination for human tumor stem cell drug sensitivity assays (190.7). Retrieved from <http://www.cms.hhs.gov/mcd/search.asp>
2. National Cancer Institute. (2003). Statement on in vitro drug sensitivity testing.

HISTORY AND REVISIONS

Date	Action
12/1/2011	<ul style="list-style-type: none">• New template design approved by MPC.
10/6/2011	<ul style="list-style-type: none">• Approved by MPC. Reformatted references; added American Society of Clinical Oncology 2011 update to 2004 guideline; stance remains unchanged (to not use CSRAs in practice).