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Medical Policy Manual

Topic: In Vitro Chemoresistance and Chemosensitivity Assays **Date of Origin:** January 1996

Section: Laboratory **Approved Date**: March 2014

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

In vitro chemoresistance and chemosensitivity assays have been investigated as a means of predicting tumor response to various chemotherapies. Thus, these assays have been used by oncologists to select chemotherapy regimens for an individual patient. A variety of assays have been developed that differ in their processing and in the technique used to measure chemotherapy sensitivity or resistance. All assays use characteristics of cell physiology to distinguish between viable and non-viable cells to quantify cell kill following exposure to a drug of interest and all involve the same four basic steps:

1. Isolation of cells
2. Incubation of cells with drugs
3. Assessment of cell survival
4. Interpretation of the results

Although a variety of assays exist to examine chemosensitivity or chemoresistance, only a few are commercially available, including:

- The Differential Staining Cytotoxicity (DiSC) assay, involves cells treated with prospective chemotherapy agent(s) and drug sensitivity is measured by the amount of hematoxylin and eosin

or fluorescein, respectively, which tumor cells selectively uptake.

- The *Ex-vivo* Analysis of Programmed Cell Death (EVA/PCD™) assay (available from Rational Therapeutics) measures both apoptotic and non-apoptotic cell death markers in tumor samples exposed to chemotherapeutic agents. Tumor specimens obtained through biopsy or surgical resection are exposed to chemotherapy agents and then a mixture of Nigrosin B & Fast Green dye with glutaraldehyde-fixed avian erythrocytes are added to the cellular suspensions. The endpoint of interest for this assay is cell death as assessed by observing the number of cells differentially stained due to changes in cellular membrane integrity.

- The thymidine incorporation assay, includes the addition of tritiated thymidine to the cell culture after 72 hours of incubation with the drug(s) of interest. By studying the inverse relationship between the amount of thymidine absorbed by viable tumor cells, drug sensitivity can be calculated.[1] The Extreme Drug Resistance assay (EDR®) (commercially available at Exiqon Diagnostics) is methodologically similar to the thymidine incorporation assay.[2] In this assay, tumor cells from an individual patient are cultured in soft agar and then exposed to high concentrations of selected chemotherapeutic agents for prolonged periods of time, far exceeding the exposure anticipated in vivo. Cell lines that survive this exposure are characterized by showing extreme drug resistance.

- The MTT assay, involves single tumor cell suspensions which are exposed to the chemical MTT. If the cell is metabolically active, blue crystals are produced. The Histoculture Drug Response Assay® (HDRA) is a type of MTT assay (commercially available from AntiCancer, Inc.) In this assay, drug sensitivity is evaluated by quantification of cell growth in the 3-dimensional collagen matrix. There is an inverse relationship between the drug sensitivity of the tumor and cell growth. Concentrations of drug and incubation times are not standardized and vary depending on drug combination and tumor type.

- The Adenosine Triphosphate (ATP) Bioluminescence Assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, then exposed to drugs. Following incubation with the drug, cultured cells are lysed and ATP generation is captured with a luminometer, a device which measures light emitted from metabolic activity. From the measurement of light, the number of viable tumor cells can be calculated. A decrease in ATP indicates drug sensitivity, whereas no loss of ATP suggests that the tumor is resistant to the agent of interest. The ChemoFX® test (Precision Therapeutics) is an example of this technology.

Results may be reported as drug sensitive, drug resistant, or intermediate. Drugs identified as drug sensitive are thought to be potentially effective in vivo chemotherapies, while drugs identified as resistant are thought to be potentially ineffective chemotherapies. The rationale for chemosensitivity assays is strongest where there are a variety of therapeutic options and there are no clear selection criteria for any particular regimen in an individual patient.

Regulatory Status

For the proprietary tests EDR and the ChemoFX assay, premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the tests are performed in a laboratory licensed by the Clinical Laboratory Improvement Act (CLIA) for high-complexity testing.

MEDICAL POLICY CRITERIA

I. In vitro chemosensitivity assays, including but not limited to the histoculture drug response assay or a fluorescent cytoprint assay, are considered **investigational.**

II. In vitro chemoresistance assays, including but not limited to extreme drug resistance assays, are considered **investigational**.

SCIENTIFIC EVIDENCE

A 2000 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment reviewed both chemosensitivity and chemoresistance assays.[3] This TEC assessment provided a detailed discussion on what type of data would be required to validate the clinical use of chemoresistance and chemosensitivity assays and considered the following methods:

- Correlation studies based on in vitro prediction of in vivo response

  A variety of studies have reported a correlation between in vitro prediction or response and clinical response. While these studies may have internal validity, they cannot answer the question of whether patients given assay-guided therapy or empiric therapy have different outcomes. For example, suppose that one group of patients is treated based on assay results and demonstrates an overall response rate of 75%. It is possible that a similar group of patients matched for important prognostic factors and given a uniform empiric chemotherapy regimen, could achieve the same overall response rate. However, if the response rates are the same for the two groups, the assay-guided group may experience more adverse effects from treatment or may have lower overall survival. The principal outcomes associated with treatment of solid organ malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome. To determine whether assay-guided treatment results in different primary health outcomes, decision analysis or comparative trials are required.

- Decision analysis

  While decision analysis is a useful tool, it may be limited when the decision tree is so complex that it is not possible to obtain evidence-based estimates for many of the probabilities in the tree. For this reason, the 2000 TEC assessment concluded that decision analysis would not be a useful tool for assessing the relative effectiveness of assay-guided and empiric treatment.

- Assessment based on direct evidence

  Given the limitations in the above two techniques, the 2000 TEC assessment focused on direct evidence that compared outcomes for patients treated either by assay-guided therapy or contemporaneous empiric therapy. A total of 7 studies were identified, none of which provided strong evidence to validate the clinical role of chemosensitivity or chemoresistance assays.

The BCBSA TEC Assessment was updated in 2002.[4] No studies were identified that address the limitations noted in the above discussion. Specifically, no studies were identified that provided direct evidence comparing outcomes for patients treated either by assay-guided therapy or contemporaneous empiric therapy.

Chemoresistance Assays

In their assessment of chemoresistance assays, the authors of a 2004 Journal of Clinical Oncology systematic review of this type of testing pointed out that the clinical utility of these assays will depend on the prior probability of response to a given chemotherapy.[5] Since chemoresistance assays are used to deselect potential chemotherapies, the negative predictive value (NPV) is the key statistical measure. NPV relates to the likelihood that chemoresistance as measured in vitro will correspond to a lack of clinical effect. Unless the negative predictive value is high, there is a chance that clinical decision-making based on a chemoresistance assay could inappropriately exclude an effective therapy. The negative predictive value will vary according to the prior probability of chemoresistance. For example, the negative predictive value in testicular cancer, typically a very chemosensitive tumor, will be lower than that associated with malignant melanoma, a very chemoresistant tumor. The TEC assessment concluded that 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) assay was specifically designed to produce a very high negative predictive value (>99%), such that the possibility of inappropriately excluding effective chemotherapy is remote in all clinical situations.[6] However, there are still inadequate clinical data to determine whether the use of EDR assays to deselect ineffective chemotherapies results in improved health benefits. While the relevant clinical outcome in chemo*sensitivity* assays focuses on improved survival, the relevant outcome associated with chemo*resistance* assays is more controversial. Advocates of the EDR assay point out that avoidance of the toxicity of ineffective drugs is the relevant outcome, while others point out that this represents an intermediate outcome and that improved patient survival is the relevant outcome for chemoresistance assays.[6] For example, in clinical practice, deselection of one chemotherapy implies positive selection of another drug that did not show chemoresistance. Therefore, the toxicity and effectiveness of the drugs that are selected as a result of the EDR assay are relevant outcomes. Finally, a related clinical outcome is the extent to which an in vitro assay can improve on the empirical performance of the physician. For example, chemoresistance typically can be predicted without the use of an EDR assay in heavily pretreated patients with refractory tumors.

The bulk of the literature regarding extreme drug resistance assays have focused on nonrandomized correlation studies and associated reviews[7] that compare results from predictive in vitro assays with observed outcomes of chemotherapy.[8-21] However, in these studies, the patients do not receive assay-guided chemotherapy regimens. As discussed in the 2004 systematic review[5], correlational studies are inadequate for several reasons. First, such studies often aggregate patients with different tumor types, disease characteristics, chemotherapy options, and probabilities of response. This process is problematic since the accuracy of each assay used to predict in vivo response probably varies across different malignancies and patient characteristics. Second, the method by which assay results are translated into treatment decisions is not standardized. Without knowing the rules for converting assay findings into treatment choices, it is impossible to determine the effects of assay-guided treatment on health outcomes. Third, 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 predication for response. A literature search found no prospective comparative studies focusing on the use of the EDR, or testing outcome with assay-directed therapy versus physician chosen therapy.

Conclusion

Current evidence is insufficient to support the use of the EDR assays for directing therapy or for prediction of outcome. Current studies are limited by retrospective design, non-comparative design and small sample size. Furthermore, tissue samples are often not sufficient to achieve evaluable results. Large, randomized, prospective clinical studies comparing outcomes between assay-directed therapy to physician-directed therapy would be required to justify use of the EDR assay in these patient populations. Initial response to assay-directed therapy and time to progression would be interesting endpoints; however, evaluation of overall and disease-specific survival, quality of life, and adverse events is critical to validate the clinical utility of this assay.

Chemosensitivity Assay

The enthusiasm for chemosensitivity assays, in general, has diminished over the years, due to the poor positive predictive values (PPV), the key statistical measure for this type of assay. PPV relates to the likelihood that drugs shown to be effective in vitro will produce a positive clinical response. For example, a meta-analysis by Von Hoff of 54 retrospective studies reported a positive predictive value of only 69%.[22] The poor positive predictive value may, in part, be related to a variety of host factors, such as tumor vascularity, poor quality of data, or tumor sampling bias. Several prospective trials have also been published, although interpretation of their findings is hindered by technical challenges, inconclusive results, or methodologic issues, which further dampened enthusiasm.[23-33] For example, using a chemosensitivity assay, Xu and colleagues compared outcomes for an assay-guided treatment group with outcomes for a group given contemporaneous empiric therapy.[26] The patient sample consisted of 156 patients with advanced breast cancer. The article stated that choice of regimen in the assay-guided group was based on assay results, but no specific decision rules were reported. Patients whose EDR results suggested resistant disease were given empiric regimens and were excluded from the analysis of outcome results, violating the principles of intention-to-treat analysis. An intention-to-treat analysis is the most robust analysis to control for bias and permits investigators to calculate the number of patients needed to test to identify one patient whose outcomes could be improved by use of assay-guided rather than empiric therapy.

In the only prospective, randomized study published since the TEC assessments, Cree and colleagues reported on a chemosensitivity assay-directed chemotherapy versus physician’s choice in patients with recurrent platinum-resistant ovarian cancer.[34] Response rate and progression-free survival were studied in 180 patients randomized to either ATP-based tumor chemosensitivity 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: 32% achieved a partial or complete response in the physician's-choice group compared with 41% in the assay-directed group (26% vs. 31% by intention-to-treat analysis, respectively). Intention-to-treat analysis showed no statistically significant differences between the groups in terms of progression-free survival (93 days in the physician's-choice group vs. 104 days in the assay-directed group), nor any difference in overall survival between the groups. 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.

Conclusion

The current evidence is insufficient to permit conclusions regarding the benefit of chemosensitivity assays to predict a positive clinical response for a specific chemotherapy. Current studies are limited by retrospective design, non-comparative design and small sample size. Large, randomized, prospective clinical studies are needed to assess how assay-directed therapy compares with physician-directed therapy in predicting positive therapy response and improving overall health outcomes.

Clinical Practice Guidelines

Several clinical practice guidelines specifically address the use of chemoresistant or chemosensitive assays, although none specifically recommend their use.

American Society of Clinical Oncology (ASCO)

In 2004, ASCO published guidelines within a technology assessment of the use of chemotherapy sensitivity and resistance assays (CSRA)[35] along with a systematic review of the literature.[5] An update to these guidelines was published in 2011.[36] The most recent guidelines concurred with the 2004 guidelines, stating a "review of the literature does not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice."

National Comprehensive Cancer Network (NCCN)

2014 NCCN guidelines for the treatment of epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer (v 1.2014) state: "Chemotherapy/resistance and/or biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy" when multiple equivalent chemotherapy options are available; however, the Category 3 level of evidence indicates "the current level of evidence is not sufficient to supplant standard-of-care chemotherapy."[37] The panel believes that in vitro chemosensitivity testing to help choose a chemotherapy regimen for recurrent disease situations should not be recommended because of the lack of demonstrable efficacy for this approach.

Summary

There is insufficient evidence in the published peer-reviewed scientific literature to determine how chemoresistance and chemosensitivity assays improve chemotherapy treatment decisions or overall health outcomes compared to physician-directed therapy. Furthermore, unexpected limitations have arisen including sampling bias due to heterogeneity of tumors and insufficient biospecimen processing resulting in unevaluable data which have limited conclusions reached in current studies. Therefore, the use of chemoresistance and chemosensitivity assays for the selection of chemotherapy treatment, or any other indication, is investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
There are no specific codes for extreme drug resistance assay, which is a multistep laboratory procedure.		
CPT	87999	Unlisted microbiology procedure
	88199	Unlisted cytopathology procedure
	89240	Unlisted miscellaneous pathology test
HCPCS	No code	