Subject: In Vitro Chemosensitivity and Chemoresistance Assays

Overview: Chemosensitivity and chemoresistance assays seek to help clinicians better choose chemotherapy treatment options for patients. The assays expose tumor cells to different chemotherapy agents and measure cellular response.

Policy and Coverage Criteria:

Harvard Pilgrim does NOT cover in vitro chemosensitivity and chemoresistance assays (including, but not limited to, the ChemoFX Assay; Oncotech ERD Assay; MiCK Assay [CorrectChemo]). They are considered investigational/experimental and unproven.

Exclusions: N/A

Supporting Information:

1. Technology Assessment: A variety of chemosensitivity and chemoresistance assays are available and in development. In vitro techniques such as differential staining cytotoxicity assays, extreme drug resistance assays, fluorescence assays, human tumor cloning assays, thymidine incorporation assays, and human tumor stem cell assays are used in tests designed to interpret cellular response to different chemotherapy agents.

2. Literature Review: Most available clinical literature does not evaluate the survival rate of patients treated with assay-directed chemotherapy regimens versus patients treated with the physician’s choice of regimen. While some studies show the assays may be useful in better selecting a chemotherapy regimen, there is not enough evidence to support the use of these tests to effectively guide treatment options.

The American Society of Clinical Oncology published an updated clinical practice guideline in 2011 reviewing chemotherapy sensitivity and resistance assays. Their review did not identify any tests for which the evidence base is strong enough to support use in oncology practice. The group did not recommend the use of the assays noting, “Oncologists should make chemotherapy treatment recommendations based on published reports of clinical trials and a patient’s health status and treatment preferences.” The group further encouraged ongoing participation in clinical trials to better evaluate these technologies.

A number of studies evaluated the clinical value of the microculture-kinetic drug-induced apoptosis assay (MiCK). Stickland et al. (2013) found chemotherapy-induced apoptosis measured by the MiCK assay demonstrated significant correlation with outcomes and appeared to be predictive of complete remission and overall survival for patients receiving standard induction chemotherapy. Salom et al. (2012) reported results of a prospective, multi-institutional and blinded trial of the assay conducted on 104 evaluable ovarian cancer patients treated with chemotherapy. The MiCK assay was performed prior to therapy, but treating physicians were not told of the results and selected treatment only on clinical criteria. Outcomes (response, time to relapse, and survival) were compared to the drug-induced apoptosis observed in the assay. Results found overall survival in primary therapy, chemotherapy naive patients with Stage III or IV disease was longer if patients received a chemotherapy which was best in the MiCK assay, compared to shorter survival in patients who received a chemotherapy that did not
perform the best. A small study by Bosserman et al. (2012) showed a significant difference in response outcomes when patients were treated with a MiCK assay-directed chemotherapy agent.

A 2010 report by Herzog et al. found the ChemoFx assay to be an independent predictor of overall survival when used to predict response to platinum chemotherapy agents. 192 patients with primary ovarian cancer underwent in vitro chemosensitivity testing on samples from their tumors. Median OS was 72.5 months for patients with tumors categorized as responsive, 48.6 months for intermittently responsive, and 28.2 months for nonresponsive.

Harry et al. (2009) discussed the role of chemosensitivity and chemoresistance assays in predicting patient response to treatment for advanced cervical and ovarian cancers. Their review of clinical studies found that while some assays can demonstrate active and inactive response, the tests do no translate into an accurate prediction of patient response and survival. The authors note there is continued debate concerning the optimal clinical applicability of the tests and further studies are needed to establish their role in clinical decision making.

A recent prospective study by Tian et al. (2014) reported improved clinical outcomes for recurrent ovarian cancer patients with chemotherapies indicated to be sensitive by a chemoresponse assay, compared with patients treated with non-sensitive therapies. 262 women with persistent or recurrent epithelial ovarian cancer were empirically treated with one of 15 therapies, blinded to assay results. Patients treated with assay-sensitive therapies had improved progression-free survival. The authors concluded that the results provide evidence that the chemoresponse assay is a predictive marker, demonstrating its ability to discern specific therapies that are likely to be more effective among multiple alternatives.

Cree et al. (2007) reported on a prospective randomized controlled trial to determine response rate and progression free survival following chemo in patients with ovarian cancer. 180 patients were treated. 94 were randomized into the group receiving assay-directed treatment. 86 received physician’s choice treatment. Evidence of response was not significantly different between the two groups and there was no significant difference in the median progression free or overall survival between the two. There was some trend towards improved response and progression-free survival for the assay-directed treatment.

Wu et al. also did not find significantly different outcomes in a study evaluating patients with gastric cancer treated with MTT-directed chemo or physician’s choice of chemotherapy. The researchers concluded the clinical benefit of the MTT chemosensitivity assay is limited.

A 2004 report by Cloven et al. evaluated the retrospective results of 5195 epithelial ovarian cancers studied to determine whether any relationship existed between histological subtypes and chemoresistance. The EDR assay was used to determine the responsiveness of each subset during exposure to standard chemotherapeutic agents. While results showed significant differences in frequency of response and biomarker expression, patient survival benefits remain unproven.

Additional studies have assessed the chemosensitivity of various cancers to chemotherapy agents with mixed results. In some retrospective studies, a trend toward increased response rates and survival has been reported. However, other studies have not shown significant differences (Tanigawa et al., 2016; Gallion et al., 2006; Kubota et al., 2006; Ugurel et al., 2006; Iwadate et al., 2005; Stabib et al., 2005; Nakada et al., 2004).

3. Professional/Governmental Agencies:

CMS: Human tumor drug sensitivity assays are considered experimental, and therefore, not covered under Medicare at this time.


Codes:

CPT:

86849 – Unlisted immunology procedure
87999 – Unlisted microbiology procedure
88299 – Unlisted cygnetogenetic study
89240 – Unlisted miscellaneous pathology test
References:

8. Kubota, T., Weisenthal, I, L. Chemotherapy sensitivity and resistance testing: to be “standard” or to be individualized, that is the question. Gastric Cancer. 2006; 161; 180-95.