In Vitro Chemoresistance and Chemosensitivity Assays

Policy Description

In vitro chemotherapy sensitivity and resistance assays refer to any in vitro laboratory analysis that is performed specifically to evaluate whether tumor growth is inhibited by a known chemotherapy drug or, more commonly, a panel of drugs (Hatok et al., 2009; Schrag et al., 2004).

Related Policies

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Policy Title</th>
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Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.*

1. In vitro chemosensitivity assays, including, but not limited to, the histoculture drug response assay or a fluorescent cytoprint assay DO NOT MEET COVERAGE CRITERIA.

2. In vitro chemoresistance assays, including, but not limited to, extreme drug resistance assays DO NOT MEET COVERAGE CRITERIA.

Scientific Background

Chemotherapy treatment recommendation has long been based on carefully designed clinical studies in large patient populations and provide an individual patient with a probability for response based on clinically observed response rates. This approach has led to major progress
in clinical oncology and has helped to identify successful therapeutic regimens for patients with many cancers. However, the response rates are relatively low, and there are still many cancers for which there is only marginal treatment. Tumor cells isolated from these patients often are resistant to a wide range of anticancer drugs. In addition, it is becoming clear that each individual patient’s tumor is genotypically and phenotypically different (Hatok et al., 2009).

Chemotherapy sensitivity and resistance assays were developed to determine if a patient with cancer might be resistant or sensitive to a specific chemotherapy treatment prior to use. A chemosensitivity assay detects the effects (cytotoxic, apoptotic, and so on) of a given chemotherapeutic agent outside an organism. The assays vary, but typically they follow the same steps: cells from the patient are isolated, incubated with the chemotherapeutic agent, and assessed for cell survival and cell response (Hatok et al., 2009; Tatar et al., 2016). This assay allows clinicians to evaluate the effects of the chemotherapeutic agent without unnecessary exposure to cells. However, there are a number of difficulties with these assays; for example, the potency of a chemotherapeutic agent may only be seen after time has elapsed. Many assays have been created to assess the potency of chemotherapeutic agents, including proprietary tests such as Chemo-FX and ChemoINTEL, as well as non-proprietary assays such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolyum bromide (MTT), adenosine triphosphate-tumor chemosensitivity (ATP-TCA), and differential staining cytotoxicity (DISC) (Tatar et al., 2016).

These assays typically rely on the use of cell cultures within the presence of the anticancer agent(s). For example, the MTT procedure involves culturing tumor cells with anticancer agents, then adding MTT, which is reduced to a blue dye in the cell. The intensity of the uptake allows the user to estimate the drug resistance of the tumor cells. DISC cultures tumor cells in three different concentrations of the drug, incubates them for 6 days, then uses differential dye staining to identify viable cells (Hatok et al., 2009). Another assay, ChemoFx (from Precision Therapeutics now merged with Helomics), exposes tumor cells to increasing doses of chemotherapeutic drugs, and the number of live cells remaining post-treatment is counted. These counts are combined into a dose-response curve, which is used to categorize a tumor’s response as “responsive,” “intermediate response,” or “non-responsive” (Brower, Fensterer, & Bush, 2008). Another proprietary test is the Microculture-Kinetic (MiCK) assay (from DiaTech Oncology, now Pierian) (Grendys et al., 2014). This test relies on drug-induced apoptosis with the quantification of tumor cells’ response to chemotherapeutic agents. This test is now branded as ChemoINTEL (Pierian, 2019).

Clinical Validity and Utility

Tatar et al (2016) conducted a study to assess three in vitro chemosensitivity assays in ovarian carcinoma. 26 patients with ovarian carcinoma contributed tumoral tissue, and three assays (the MTT assay, the ATP-TCA assay, and the DISC assay) were used to evaluate the chemosensitivity of paclitaxel, carboplatin, docetaxel, topotecan, gemcitabine, and doxorubicin. The authors stated that all three assays correlated reasonably well with each other and are “particularly useful for serous and advanced cancers”. However, they caution that “large prospective studies comparing standard versus assay-directed therapy with an endpoint of overall survival are required before routine clinical utilization of these assays (Tatar et al., 2016).”

Kwon et al (2016) evaluated the usefulness of the in vitro adenosine triphosphate-based chemotherapy response assay (ATP-CRA) for prediction of clinical response to fluorouracil-based adjuvant chemotherapy in stage II colorectal cancer. Tumor specimens of 86 patients with stage II colorectal adenocarcinoma were tested for chemosensitivity to fluorouracil, and chemosensitivity was determined by cell death rate (CDR) of the drug-exposed cells. 11 of the 86 patients had a recurrence, and the group with CDR ≥20% was associated with better disease-free survival than the group under 20%. The authors concluded that “in stage II colorectal cancer, the in vitro ATP-CRA may be useful in identifying patients likely to benefit from fluorouracil-based adjuvant chemotherapy (Kwon et al., 2016).”
Krivak et al (2014) conducted an observational study to evaluate if the ChemoFx assay can identify patients who are platinum-resistant prior to treatment. 276 women with International Federation of Gynecology and Obstetrics stage III-IV ovarian, fallopian, and peritoneal cancer were enrolled, and the responsiveness of their tumors was evaluated. All patients were treated with a platinum/taxane regimen following cytoreductive surgery. The authors found that the patients whose tumors were resistant to carboplatin were at increased risk of disease progression compared to those who were nonresistant. The authors stated that “assay resistance to carboplatin is strongly associated with shortened PFS among advanced-stage epithelial ovarian cancer patients treated with carboplatin + paclitaxel therapy, supporting use of this assay [ChemoFx] to identify patients likely to experience early recurrence on standard platinum-based therapy (Krivak et al., 2014).”

Rutherford et al (2013) conducted a prospective study evaluating the use of ChemoFx assay in recurrent ovarian cancer patients. 252 women with persistent or recurrent ovarian cancer were enrolled and fresh tissue samples were collected for chemoresponse testing. Patients were treated with one of 15 protocol-designated treatments empirically selected by the oncologist, blinded to the assay results. Patients were prospectively monitored for progression-free survival (PFS) and overall survival (OS). Patients treated with an assay-sensitive regimen demonstrated significantly improved PFS and OS while there was no difference in clinical outcomes between intermediate and resistant groups. The researchers concluded that the “study demonstrated improved PFS and OS for patients with either platinum-sensitive or platinum-resistant recurrent ovarian cancer treated with assay-sensitive agents (Rutherford et al., 2013).”

Hoffman (2018) conducted a study investigating the clinical correlation of histoculture drug response assay (HDRA) in 29 advanced gastric and colon cancer patients. The authors revealed that all 29 were being treated with drugs considered “ineffective” by the HDRA. However, nine patients were also being treated with drugs identified as “effective” by the HDRA, and these patients showed response or arrest of disease progression. The authors investigated another subset of 32 patients treated with mitomycin C and 5-fluorouracil (5-FU) and whom had advanced gastric cancer. Ten patients were identified as “sensitive” to these drugs, and their survival rates were higher than the other 22 whose tumors were “insensitive”. A separate 128-patient subset had their tumors evaluated by the HDRA, and the overall and disease-free survival rate was higher for the sensitive group compared to the resistant group. Overall, both “sensitive” groups experienced higher survival rates.

Strickland et al evaluated the correlation of the MiCK assay with patient outcomes in initial treatment of adult acute myelocytic leukemia. 109 patients with untreated AML contributed samples for the MiCK assay. The amount of apoptosis was measured over 48 hours and standardized to “kinetic units” of apoptosis (KU). The authors observed that complete remission (CR) was “significantly” higher in patients with high idarubicin-induced apoptosis (>3 KU) compared to patients with <3 KU. A multivariate analysis indicated the only significant variable to be idarubicin-induced apoptosis. The authors concluded, “Chemotherapy-induced apoptosis measured by the MiCK assay demonstrated significant correlation with outcomes and appears predictive of complete remission and overall survival for patients receiving standard induction chemotherapy (Strickland et al., 2013).”

**Guidelines and Recommendations**

**American Society of Clinical Oncology (ASCO)**

The 2011 clinical practice guideline update (Burstein et al., 2011) states 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.”

**National Comprehensive Cancer Network (NCCN)**

The NCCN Practice Guidelines in Oncology for Ovarian Cancer (NCCN, 2019) state that: “chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions to aid in situations where multiple equivalent chemotherapy options available. However, the current level of evidence is not sufficient to replace standard of care chemotherapy”. This is a category 3 recommendation (based on any level of evidence but reflects major disagreement).

Chemosensitivity/resistance testing is not mentioned in the guidelines for gastric, colon, leukemia, or prostate cancers (NCCN, 2019).

**State and Federal Regulations, as applicable**

A search for “chemoresistance” and “chemosensitivity” yielded zero results on June 14, 2019 (FDA, 2019). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
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<tr>
<td>81535</td>
<td>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</td>
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<tr>
<td>81536</td>
<td>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 (List separately in addition to code for primary procedure)</td>
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<td>86849</td>
<td>Unlisted immunology procedure</td>
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<tr>
<td>88104</td>
<td>Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation</td>
</tr>
<tr>
<td>88199</td>
<td>Unlisted miscellaneous pathology test</td>
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<tr>
<td>88305</td>
<td>Level IV - surgical pathology, gross and microscopic examination</td>
</tr>
<tr>
<td>88313</td>
<td>Special stain including interpretation and report; Group II, all other (eg, iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry</td>
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<tr>
<td>88358</td>
<td>Morphometric analysis; tumor (eg, DNA ploidy)</td>
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<tr>
<td>89050</td>
<td>Cell count, miscellaneous body fluids (eg, cerebrospinal fluid, joint fluid), except blood;</td>
</tr>
<tr>
<td>89240</td>
<td>Unlisted cytopathology procedure</td>
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</tbody>
</table>
| 0083U       | Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug
Evidence-based Scientific References


FDATA. (2019).


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