Corporate Medical Policy

In Vitro Chemoresistance and Chemosensitivity Assays AHS- G2100

Description of Procedure or Service

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).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

In vitro chemoresistance and chemosensitivity assays are considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When In Vitro Chemoresistance and Chemosensitivity Assays are covered

Not applicable

When In Vitro Chemoresistance and Chemosensitivity Assays are not covered

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

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

Policy Guidelines

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
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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 cancer might be resistant or sensitive to a specific chemotherapy treatment before being offered to a patient. Tumor cells, obtained during surgical removal of a patient’s tumor, are tested for resistance and sensitivity to predict how the tumor will respond to chemotherapy.

Clinical Validity and Utility

Herzog and Armstrong (2018) concluded that “in vitro assays of chemosensitivity or resistance, such as the Chemo-FX assay or the Extreme Drug Resistance (EDR) assay, are laboratory tests that have been developed as a method to select the optimal chemotherapy regimen (sensitivity assays) or identify those agents least likely to be effective (resistance assays). However, the utility of these assays has not been prospectively validated, and cost benefits have not been clearly demonstrated.”

Tatar et al (2016) conducted a study “to determine the efficacy of in vitro chemosensitivity assays in ovarian carcinoma and to measure the correlation of three leading assays.” They assayed “tissue samples of 26 newly diagnosed primary ovarian cancer patients with 3-(4,5-dimeth-ylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, adenosine triphosphate-tumor chemosensitivity assay (ATP-TCA) and differential staining cytotoxicity (DISC) assays. Chemosensitivity of tumors were studied for paclitaxel, carboplatin, docetaxel, topotecan, gemcitabine, and doxorubicin with each of the three assays.” They found that “The in vitro chemosensitivity results of MTT, ATP, and DISC assays were found to be similar.” They concluded that “In vitro chemosensitivity can be determined in ovarian carcinoma with ATP, MTT, or DISC assays before the initiation of chemotherapy. These three assays correlate well with each other and are particularly useful for serous and advanced cancers. Large prospective studies comparing standard versus assay-directed therapy with an endpoint of overall survival are required before routine clinical utilization of these assays.”

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 pathologically confirmed stage II colorectal adenocarcinoma were tested for chemosensitivity to fluorouracil.” They found 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.”

Krivak et al (2014) conducted an observational study to evaluate if a chemoresponse 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 using a chemoresponse assay. All patients were treated with a platinum/taxane regimen following cytoreductive surgery. 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 to identify patients likely to experience early recurrence on standard platinum-based therapy.”

Rutherford et al (2013) conducted a prospective study evaluating the use of a chemoresponse 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.”

Hoffman (2018) conducted a study investigating the clinical correlation of histoculture drug response assay in 29 advanced gastric and colon cancer patients they found that “In one study, 29 patients were treated with drugs shown to be ineffective in the HDRA, and all 29 cases showed clinical chemoresistance. In nine patients treated with drugs shown to be effective in the HDRA, six showed
clinical chemoresponse and three showed arrest of disease progression. In a study of 32 patients with stage III and IV gastric cancer treated with mitomycin C and 5-fluorouracil (5-FU), the survival rate of 10 patients whose tumors were sensitive to either mitomycin C and/or 5-fluorouracil in the HDRA was significantly better than that of 22 patients whose tumors were insensitive to both drugs in the HDRA. Twenty-nine patients with stage III and IV colorectal cancer without remaining measurable tumor lesions after surgery were treated with fluoropyrimidines adjuvantly. The recurrence-free survival rate of 7 patients whose tumors were sensitive to 5-fluorouracil in the HDRA was significantly better than that of 22 patients whose tumors were insensitive in the HDRA. In a companion study of 128 gastric cancer patients whose tumors were evaluated in the HDRA, the overall and disease-free survival rates of the HDRA-sensitive group were found to be significantly higher than those of the HDRA-resistant group, treated with the same drugs.”

State and Federal Regulations, as applicable
Commercially available chemosensitivity and chemoresistance assays are laboratory developed tests (LDT); developed, validated and performed by individual laboratories.
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.

Practice Guidelines and Position Statements
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, 2018) 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). The NCCN panel also stated that in vitro chemo sensitivity testing to choose a chemotherapy regimen for recurrent disease should not be recommended due to lack of demonstrated efficacy (Karam, Chiang, Fung, Nossov, & Karlan, 2009; Matsuo, Eno, Im, Rosenshein, & Sood, 2010)

Chemosensitivity/resistance testing is not mentioned in the guidelines for gastric, colon, leukemia, or prostate cancers (NCCN, 2017).

Billing/Coding/Physician Documentation Information
This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0083U, 81535, 81536, 86849, 88104, 88199, 88305, 88313, 88358, 89050, 89240,

ICD-10 Codes- All within range C00.0-D09.9
BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


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Medical Director review 11/2019


Medical Director review 4/2020

Policy Implementation/Update Information

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<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>1/1/2019</td>
<td>New policy developed. In vitro chemoresistance and chemosensitivity assays are considered investigational for all applications. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)</td>
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<td>12/10/19</td>
<td>Reviewed by Avalon 3rd Quarter 2019 CAB. Coding table removed and CPT code 0083U added to Billing/Coding section. No change to policy statement. Medical Director review 11/2019. (lpr)</td>
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<tr>
<td>5/26/20</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.