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Corporate Medical Policy

In Vitro Chemoresistance and Chemosensitivity Assays AHS- G2100

File Name:	in_vitro_chemoresistance_and_chemosensitivity_assays
Origination:	1/1/2019
Last CAP Review:	3/2021
Next CAP Review:	3/2022
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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 not covered. BCBSNC will not reimburse for non-covered 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

Reimbursement is not allowed for in vitro chemosensitivity assays, including, but not limited to, the histoculture drug response assay or a fluorescent cytoprint assay.

Reimbursement is not allowed for in vitro chemoresistance assays, including, but not limited to, extreme drug resistance assays.

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

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. 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 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 ChemoFX 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). Several proprietary assays exist, such as ChemoFX (from Precision Therapeutics now merged with Helomics), which 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). A third proprietary test comes from RGCC, titled "Onconomics". This test evaluates both molecular markers and viability assessments to determine efficacy of certain drugs. However, this test does follow the same pattern as the previously discussed tests; developing cell cultures and examining effects of chemotherapeutic agents on their population (RGCC, 2020).

Clinical Validity and Utility

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-diphenyltetrazolyum 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.”

Strickland et al. evaluated the correlation of the MiCK assay with patient outcomes in initial treatment of adult acute myelocytic leukemia (AML). 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).

Howard et al. developed and assessed a “chemopredictive” assay (ChemoID), which was intended to identify the most effective chemotherapy out of a panel of selected treatments. ChemoID evaluates the efficacy of chemotherapies using a patient’s live tumor cells, as well as the cancer stem cells (CSC) that are purported to cause recurrence in patients. 42 glioblastoma patients were included and were treated with standard of card temozolomide (TMZ). Clinical outcomes such as “tumor response, time to recurrence, progression-free survival (PFS), and overall survival (OS). Odds ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes” were estimated. The authors found that for every 5% increase in CSC kill by TMZ, 12-month patient response (defined as “nonrecurrence of cancer”) increased by 2.2-fold. The authors also identified a less significant association with the bulk tumor cells; a 5% increase in bulk tumor cell kill corresponded with a 2.75-fold increase in nonresponse ($p = .07$). At

>40% cell kill for CSC and >55% cell kill for bulk tumor cells, the area under curve was 0.989. Median recurrence time was 20 months for patients with a positive (defined as >40%) CSC test, compared to 3 months for patients with a negative test. Similarly, median recurrence time was 13 months for patients with a positive bulk tumor cell test (>55%), compared to 4 months for a negative test. Finally, the ChemoID CSC results were found to "potentially" identify more optimal treatments in 34 patients, while the bulk tumor results may have resulted in more optimal treatments in 27 patients. Overall, the authors concluded that "the ChemoID CSC drug response assay has the potential to increase the accuracy of bulk tumor assays to help guide individualized chemotherapy choices" (Howard et al., 2017).

State and Federal Regulations, as applicable

Searches for "chemoresistance" and "chemosensitivity" yielded zero results on July 6, 2020 (FDA, 2020). 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.

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)

National Comprehensive Cancer Network (NCCN, 2020a, 2020b)
The NCCN Practice Guidelines in Oncology for Ovarian Cancer (NCCN, 2020b) state that: "chemosensitivity/resistance and/or other biomarker assays are being used at some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant 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, or prostate cancers (NCCN, 2020a).

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

Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

Medical Director review 10/2020

Specialty Matched Consultant Advisory Panel 3/2021

Medical Director review 3/2021

Policy Implementation/Update Information

1/1/2019	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)
12/10/19	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)
5/26/20	Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statement. (lpr)
11/10/20	Reviewed by Avalon 3rd Quarter 2020 CAB. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. Updated references and policy guidelines section. Literature review. Medical Director review 10/2020. (lpr)
4/6/21	Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)