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| MEDICAL POLICY | Chemoresistance and Chemosensitivity Assays |
| Effective Date: 12/1/2021 | Medical Policy Number: 121 |
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| Medical Officer Date | Technology Assessment Committee Approved Date: 2/00; 2/01; 3/02; 3/03;1/08; 10/10; 11/12; 10/14; 11/14; 10/15; 12/16; 2/18; 8/19; 03/2020; 05/2021; 09/2021 |

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Aycin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

I. Chemoresistance and chemosensitivity assays are considered **investigational and are not covered** in the treatment of cancer. Examples of non-covered tests include, but are not limited to the following (A.-G.):

- A. BioSpeciFx®
- B. ChemoFX®
- C. CorrectChemo®
- D. Ex-Vivo Analysis of Programmed Cell Death (EVA-PCD)
- E. Histoculture Drug Response Assay®
- F. Oncotech Extreme Drug Resistance [EDR] Assay for Solid Tumor®
- G. 3D Predict Glioma (KIYATEC®, Inc)

Link to [Policy Summary](#)

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CPT CODES

| All Lines of Business | |
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| Not Covered | |
| 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 combinations |
| 0248U | Oncology (brain), spheroid cell culture in a 3D microenvironment, 12 drug panel, tumor-response prediction for each drug |
| 81535 | 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 |
| 81536 | 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) |
| Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be denied as not covered . | |
| 86849 | Tissue Typing Immunological Procedures |
| 87999 | Unlisted microbiology procedure |
| 88299 | Unlisted cytogenetic study |
| 89240 | Unlisted miscellaneous pathology test |

DESCRIPTION

Protocols for treating cancer are currently based on the type and stage of the cancer. Chemoresistance and chemosensitivity (e.g., Oncotech Assays and Chemo FX Assay) tests have been proposed as a method predicting the effect of specific drugs on tumors in order to assist in chemotherapy selection. However, current evidence has not demonstrated that these tests have been used to alter treatment decisions which have led to improved health outcomes.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of chemoresistance and chemosensitivity assays as a method of selecting chemotherapeutic treatment for cancer. Below is a summary of the available evidence identified through February 2021.

Systematic Reviews

In 2020, Hayes assessed the validity and utility of the ChemoFx Assay (Helomics).¹ No studies assessed the analytical validity of the current commercial version of the ChemoFx test in its entirety. Two studies reported failures in the in vitro cell culture (1 step in the test's process) and 1 study reported unspecified quality control issues, each in a small proportion of samples. Evidence from 4 very-poor-quality studies suggested that patients treated with ChemoFx test-sensitive chemotherapies are likely to have improved progression-free or overall survival. However, the strength of the association is weak and limitations in study design and execution, including patient overlap between studies, use of simulated data, and a focus on ovarian and related cancers (e.g., fallopian tube cancer and primary peritoneal cancer), constitute insufficient evidence that the ChemoFx test results are highly likely to predict a patient's response to a given chemotherapeutic agent. No peer-reviewed studies were identified that addressed the clinical utility of the ChemoFx test.

Investigators concluded that there is a very-low-quality body of evidence for the ChemoFx test, an in vitro patient tumor-derived cell culture assay that determines how cancer cells may respond to chemotherapeutic agents in order to help guide physicians' treatment decisions in patients with gynecologic cancer. The evaluated studies provided very-low-quality clinical validity evidence that showed weak associations between the results of the ChemoFx assay and patient survival. These studies also lacked a strong study design and execution, which further reduced confidence that the ChemoFx test could accurately assist with treatment selection. Hayes ultimately assigned a "D2" rating (insufficient evidence) for the use of the ChemoFx test.

Nonrandomized Studies

- A 2015 literature review by Richard and colleagues on the use of the ChemoFX assay to identify effective treatment for epithelial ovarian cancer suggest that the assay is an effective option for improving patient outcomes.² However, authors indicated that the evidence remains limited by the lack of comparison between multiple therapies and other factors such as the possibility of toxicity that were not addressed.
- In 2013, Rutherford et al. published a prospective study evaluating the clinical relevance of a chemoresponse assay in the treatment of persistent or recurrent ovarian cancer.³ A total of 262 patients were treated with one of fifteen treatments prescribed by the oncologist. Chemoresponse assays were performed and classified treatment as sensitive (S), intermediate (I), or resistant (R). Results indicate that patients treated with an assay-sensitive treatment had an improved clinical outcome (mean overall survival was increased by 14 months; 37.5 months for S vs. 23.9 months for I+R, $p=0.010$); however, this study did not evaluate how assay results were used to alter treatment decisions or improve progression-free or overall survival. Although this and other studies may establish the clinical validity of chemoresponse assays by demonstrating a correlation of response to test results, current evidence does not show how assay-guided therapy may be used to alter outcomes.

Additional studies have been identified which are limited by a non-randomized design, small sample size and short-term follow-up.^{4,5}

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The NCCN clinical practice guidelines for ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) (v.2.2021) principles of systemic therapy have a general information bullet that stated:⁶

- 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 (category 3).

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

No other NCCN guidelines were identified that referenced chemosensitivity/chemoresistance assays.

American Society of Clinical Oncology (ASCO)

The 2011 ASCO clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays recommends that the assays be used only in the clinical trial setting.⁷

CENTERS FOR MEDICARE & MEDICAID

As of 08/30/2021, the following Centers for Medicare & Medicaid (CMS) coverage guidance was identified which also consider chemoresistance and chemosensitivity assays investigational:

- National Coverage Determination (NCD) for Human Tumor Stem Cell Drug Sensitivity Assays ([190.7](#))
- Local Coverage Determinations (LCDs): Lab: Special Histochemical Stains and Immunohistochemical Stains ([L36353](#)) and In Vitro Chemosensitivity & Chemoresistance Assays ([L37630](#))
- For the 3D Predict Glioma test, by Kiyatec®, Inc. (South Carolina): Local Coverage Determination (LCD): In Vitro Chemosensitivity & Chemoresistance Assays ([L34554](#))

POLICY SUMMARY

The current evidence is insufficient to support the use of chemoresistance or chemosensitivity assays for patients with or without cancer. There is a lack of studies that demonstrate that these assays positively impact patient care and treatment outcomes. In addition, no evidence-based clinical practice guidelines were identified which support the use of these assays for any population.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

REFERENCES

1. Hayes Inc. ChemoFx Assay (Helomics). <https://evidence.hayesinc.com/report/gte.chemofx1700>. Published 2020. Accessed 3/22/2021.
2. Richard S, Wells A, Connor J, Price F. Use of ChemoFx(R) for Identification of Effective Treatments in Epithelial Ovarian Cancer. *PLoS Curr.* 2015;7. <https://www.ncbi.nlm.nih.gov/pubmed/26213638>
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5. Jamal BT, Grillone GA, Jalisi S. Chemoresponse Assay in Head and Neck Cancer Patients: A Three-Year Follow Up. *J Clin Diagn Res.* 2017;11(5):XC01-XC03. <https://www.ncbi.nlm.nih.gov/pubmed/28658890>
6. National Comprehensive Cancer Network (NCCN). Ovarian Cancer - Including Fallopian Tube Cancer and Primary Peritoneal Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Published 2021. Accessed 3/22/2021.
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