Easy Choice Health Plan

Missouri Care

'Ohana Health Plan, a plan offered by WellCare Health Insurance of Arizona

OneCare (Care1st Health Plan Arizona, Inc.)

Staywell of Florida

WellCare (Arizona, Arkansas, Connecticut, Florida, Georgia, Illinois, Kentucky, Louisiana, Mississippi, Nebraska, New Jersey, New York, South Carolina, Tennessee, Texas)

WellCare Prescription Insurance

WellCare Texan Plus (Medicare – Dallas & Houston markets)

In Vitro Chemosensitivity and Chemoresistance Assays (E/I)

Policy Number: HS-061

Original Effective Date: 11/20/2008

Revised Date(s): 11/24/2009; 11/12/2010; 10/6/2011; 11/1/2012; 11/7/2013; 11/6/2014; 11/5/2015; 11/3/2016; 9/7/2017; 9/6/2018

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations, and any state-specific Medicaid mandates. Links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change. Lines of business are also subject to change without notice and are noted on www.wellcare.com. Guidelines are also available on the site by selecting the Provider tab, then "Tools" and "Clinical Guidelines".

BACKGROUND

In vitro assays are intended for use with clinical decision-making to guide the pretherapeutic selection of chemotherapeutic agents. It is presumed that drugs deemed most effective or least effective in vitro can be identified prospectively by how effective they are in an in vitro test. There are a variety of in vitro assays, but they share four basic steps: isolation of tumor cells, incubation of cells with drugs, assessment of cell survival, and interpretation of result. In vitro extreme drug resistance (EDR) assays differ from in vitro drug sensitivity assays. While drug sensitivity assays presumably help the physician select an active chemotherapy agent, EDR assays predict drugs for which the tumor is extremely resistant. Reportedly, EDR effectively eliminates from consideration drugs to which the patient has a less than 1% chance of benefiting if administered the drug. The identification of ineffective chemotherapeutic agents helps prevent unnecessary patient exposure to toxic agents and eliminates the cost of inactive chemotherapy.

There is a paucity of clinical studies that investigate the value of chemoresistance assays for the selection of chemotherapy. The peer-reviewed, published medical and scientific literature includes only one small (n=66) uncontrolled case series in which chemoresistance assay results were used to select patient treatment and survival was the primary trial end-point. The

literature has significant methodological weaknesses, which make it inadequate for determining the efficacy of basing cancer chemotherapeutic treatment decisions on the results of in vitro chemoresistance assays. The major limitation in the literature is the absence of randomized controlled trials evaluating the survival rate of patients treated with assay-directed regimens compared with that of a control group treated with an empiric regimen. The preponderance of the evidence regarding chemoresistance assays is derived from correlational trials that do not use intent-to-treat analysis or investigate survival rates. Although correlational studies may provide interesting insights, they are not an adequate test of the hypothesis that pre-therapeutic decisions informed by in vitro EDR assay results affect better patient outcomes than decisions not so informed. Therefore, the results of these correlational trials have not been considered when determining the HAYES Rating for chemoresistance assays. Although proponents of EDR assay testing contend that the benefits of chemoresistance testing can be demonstrated in mathematical models, critics contend that the only relevant outcome is improved patient outcome. In the clinical setting, the potential role of chemoresistance assays would vary according to the assay feasibility, tumor type, the role of chemotherapy, and the therapeutic agents tested. The prevailing peer-reviewed medical literature is inadequate for demonstrating the efficacy of these assays.

The available literature contained five prospective studies that met the criteria for detailed review and that evaluated in vitro chemosensitivity testing for small-cell lung cancer, non-small-cell lung cancer, or ovarian cancer. In these studies, patients were non-randomly assigned to either standard therapy or to chemotherapy based on in vitro chemosensitivity testing. Patients assigned to standard therapy were primarily those from whom tumor cells could not be cultured, which was the case for between 55% and 81% of patients. For the purposes of comparing results from patients who did and did not have chemotherapy guided by chemosensitivity testing, the outcome measures were response to therapy, either tumor or clinical response, and survival. These studies provided little evidence that patient outcomes improve when in vitro chemosensitivity testing guides the selection of chemotherapeutic agents. Two of the studies reported no improvement in tumor response for patients who were treated on the basis of in vitro chemosensitivity, compared with those who were treated with standard chemotherapeutic regimens. One study reported a trend toward improved tumor response that did not achieve statistical significance, while another study reported that chemotherapy guided by chemosensitivity testing provided a statistically significant increase in tumor response. Of the three studies that provided data on patient survival, only one study documented a positive effect of in vitro chemosensitivity testing on survival. In this study, part of a cohort of previously untreated patients in relatively early stages of small-cell lung cancer underwent secondary chemotherapy guided by chemosensitivity testing.

There is insufficient evidence from the available studies to conclude that in vitro chemosensitivity testing leads to improved patient management or health outcomes. Only one of the five available studies reported a survival benefit associated with chemotherapy based on in vitro chemosensitivity testing, when compared with chemotherapy based on standard regimens or clinical indicators. In addition, all of the studies reported that tumor cells could be successfully cultured in only a small percentage of patients (Hayes, 2000 and 2003). Due to the insufficient evidence regarding both assays, they are considered experimental and investigational and NOT a covered benefit.

Professional Statements

The National Cancer Institute (2003) stated that although scientists are investigating in vitro drug sensitivity testing for cancer therapy, the current evidence does not justify routine use of this research tool for patients. The NCI has concluded that, at present, this testing is too cumbersome and expensive, and it does not provide additional benefits compared with the knowledge and judgment of experienced clinicians.

The American Society of Clinical Oncology (2004) stated 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”. A 2011 update to the American Society of Clinical Oncology clinical practice guideline maintains that evidence is insufficient to support use of CSRAs in oncology practice and not recommended outside of the clinical trial setting (Burstein, Mangu, Somerfield, Schrag, Samson, Holt, & et al, 2011). description and general information about the procedure, test, etc.

POSITION STATEMENT

Applicable To:

- ☑ Medicaid – All Markets
- ☑ Medicare – All Markets

In vitro chemosensitivity and in vitro chemoresistance assays **are considered experimental and investigational and are NOT a covered benefit.**

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CODING

Non-Covered CPT®* Codes – This list may not be all inclusive

88299†	Unlisted cytogenetic study when billed for chemoresistance or chemosensitivity assays. **†**Experimental/Investigational/Unproven and not covered when used to report in vitro chemoresistance or chemosensitivity assays.
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)
84999	Unlisted chemistry procedure
86849	Unlisted immunology procedure [when specified as in vitro chemosensitivity or in vitro chemoresistance assay, ex vivo analysis of programmed cell death]
87999	Unlisted microbiology procedure [when specified as in vitro chemosensitivity or in vitro chemoresistance assay]
8819989240	Unlisted cytopathology procedure [when specified as in vitro chemosensitivity or in vitro chemoresistance assay] Unlisted miscellaneous pathology test [when specified as in vitro chemosensitivity or in vitro chemoresistance assay]

Non-Covered HCPCS Codes – No applicable codes.

Non-Covered ICD-10-CM Diagnosis Codes – All diagnoses are non-covered.

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES

1. Burstein HJ, Mangu PB, Somerfield MR, Schrag D, Samson D, Holt L, et al. American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. *Journal of Clinical Oncology.* 2011; *29*(24): 3328-3330.
2. National coverage determination for human tumor stem cell drug sensitivity assays (190.7). Centers for Medicare and Medicaid Services Web site. http://www.cms.hhs.gov/mcd/search.asp. Published July 1, 1996. Accessed August 23, 2018.
3. Local coverage determination for chemoresistance or chemosensitivity assays (L34554). Centers for Medicare and Medicaid Services Web site. http://www.cms.hhs.gov/mcd/search.asp. Published August 23, 2018.
4. Local coverage determination for chemoresistance or chemosensitivity assays (L36634). Centers for Medicare and Medicaid Services Web site. http://www.cms.hhs.gov/mcd/search.asp. Published August 23, 2018.

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

Date	Action
9/6/2018, 9/7/2017, 11/3/2016, 11/5/2015	• Approved by MPC. No changes.
11/6/2014	• Approved by MPC. Inclusion of non-covered ICD-10 codes.
11/7/2013, 11/1/2012	• Approved by MPC. No changes.
12/1/2011	• New template design approved by MPC.
10/6/2011	• Approved by MPC. Reformatted references; added American Society of Clinical Oncology 2011 upd to 2004 guideline; stance remains unchanged (to not use CSRAs in practice).

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