

Local Coverage Determination (LCD): In Vitro Chemosensitivity & Chemoresistance Assays (L37628)

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Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
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LCD Information

Document Information

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Source Proposed LCD

DL37628

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N/A

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Notice Period Start Date

08/23/2018

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CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862 (a)(1)(A) allows coverage and payment for only those services that are

considered to be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Title XVIII of the Social Security Act, §1862(a)(1)(D) Investigational or Experimental.

Title XVIII of the Social Security Act, §1862(a)(7) excludes routine physical examinations.

42 CFR 410.32(d)(3) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet-Only Manual, Pub 100-03, *Medicare National Coverage Determinations Manual*, Chapter 1, Part 3, §190.7, Human Tumor Stem Cell Drug Sensitivity Assays.

CMS Internet-Only Manual, Pub 100-08, *Medicare Program Integrity Manual*, Chapter 3, §3.2.3.7, Special Provisions for Lab Additional Documentation Requests.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a noncoverage policy for the chemosensitivity and chemoresistance assays (CSRAs).

Summary of Evidence

CSRAs

In order to avoid ineffective chemotherapy toxicity, the intent of chemosensitivity and chemoresistance assays is to assist oncologists with the selection of chemotherapy drugs at initial diagnosis and tumor recurrence.

Chemosensitivity Assays

A chemotherapy sensitivity assay determines if a tumor growth is inhibited by a known chemotherapy drug or drug combination. Thus, the intent of the chemosensitivity assay is to assist the oncologist with effective chemotherapy agent selection.

Other names for chemosensitivity assays include non-clonogenic or clonogenic cytotoxic drug resistance assays, tumor stem cell assays, human tumor stem cell drug sensitivity assays and differential staining cytotoxic assays. The available chemosensitivity assays listed in this policy isolate tumor cells, incubate the cells with drugs, and evaluate and interpret cell survival. The difference in these assays is determined by the processing method.

Chemosensitivity assays include, but are not limited to, the following:

- DiSC assay (Differential staining cytotoxicity assay) – an *in vitro* study for hematologic malignancies. Malignant mononuclear cells are incubated with specific chemotherapeutic agents for 4 days, and then exposed to vital stain to prevent dead/dying cells from counterstaining with hematoxylin and eosin. Slides are prepared and examined by light microscopy for percent cell kill compared to untreated controls.
- ATP (Adenosine Triphosphate) assay - involves seeding known concentrations of tumor cells into microplate wells with single and combination chemotherapeutic agents. The ATP content of each well is measured after

multiple days of incubation followed by addition of luciferin-luciferase to an aliquot of lysed cells in a luminometer. Luminescence measurements are directly related to ATP levels. These measurements allow determination of percent inhibition compared to controls.

- MTT (Methyl Thiazolyl Tetrazolium) assay - determines the ability of viable cells to convert a soluble tetrazolium salt (MTT) into an insoluble formazan precipitate. Drug-induced cell death and loss of enzymatic activity generate the formazan product from the MTT.
- HDRA[®] (AntiCancer Inc) Assay - a semi-automated histoculture drug response assay utilizing the MTT stain to assess drug sensitivity.
- EVA-PCD[®] (Rational Therapeutics) assay - a non-proliferative assay that provides a measure of drug-induced cell death *in vivo*.

Chemoresistance Assays

A chemoresistance assay determines “extreme drug resistance” when tumor cell cultures are exposed to high concentrations of selected agent(s) for long exposure times. A chemoresistance assay is used to deselect potentially ineffective therapeutic agents. A single chemoresistance assay is addressed in this policy:

- Oncotech EDR[®] (Exiqon Diagnostics) - an *in vivo* assay designed to predict the sensitivity and resistance of solid tumor cultures to a variety of increasing doses of selected chemotherapy agents. Fresh viable tumor tissue is minced and enzyme digested to disaggregate the tumor cells. The tumor cells are plated in soft agar. The cells are exposed to tumor type-specific anti-neoplastic agents for five days. Drug exposures in excess of the maximum clinically tolerated are used (5 to 80 times greater than *in vivo*). Tritiated thymidine is added during the last two days of culture as a measure of cell proliferation. Treated cells are compared to untreated controls. If malignant cells proliferate *in vitro* under extreme chemotherapeutic exposure, then *in vivo* exposures will be ineffective. Results are reported as low (LDR), intermediate (IDR) and extreme drug resistance (EDR). The live cells remaining post-treatment are enumerated microscopically and the resulting cell counts are compared to controls to generate a dose-response curve for each tested agent. The response curve is used to score a tumor’s response.

Studies

The Blue Cross and Blue Shield Association (BCBSA) performed an extensive literature review that will not be cited in this policy on CSRA. Their findings, published as a Tec Assessment in 2002, indicated that there was insufficient data to determine whether assay-directed chemotherapy improves health outcomes compared to empiric chemotherapy. In summary, the authors stated that well-designed trials were needed to determine whether assay-directed chemotherapy actually improves health outcomes.

Two years later, the American Society of Clinical Oncology (ASCO) collaborated with BCBSA to assess the scientific literature in support of CSRA assays. Absent new evidence of clinical utility, ASCO recommended that CSRA should not be used outside of the clinical trial setting. A second BCBSA assessment noted a higher response rate for assay-guided therapy. However, they questioned if difference was attributed to bias and confounding.

A retrospective study suggested improved progression free (PFS) and overall survival (OS) in 50 consecutive platinum-sensitive ovarian cancer patients who received EDR assay-guided therapy. Study flaws include absence of blinding or randomization, small study size, and performance bias and selection. Therefore, the study does NOT establish the relative effectiveness of assay-guided treatment over empiric treatment. The authors acknowledged the study lacked adequate power for hypothesis testing and was intended for “exploratory purposes” to generate a hypothesis worthy of further study.

Additional studies after the BCBSA’s and ASCO’s assessments included a prospective blinded study on 48 patients with recurrent malignant glioma. While shortened time to progression and OS were noted, the findings were not

statistically significant. The authors recommended future studies.

Using an ATP-based assay (not EDR), 147 platinum resistant patients with ovarian cancer were randomized between assay-directed chemotherapy vs physician's choice of therapy. While improved PFS response rates were noted, there was no difference in OS between the groups. These authors recommended a larger trial.

In another study, the EDR assay results were available for 189 non-small cell lung cancer patients for the oncologist's consideration for assay-directed therapy. In 59 of 189 patients who received post-op or adjuvant therapy, Eastern Cooperative Oncology Group (ECOG) standard or the oncologist's preference determined the therapy. The selected therapy was "not individualized to each patient with respect to assay results". Forty five (45) patients were assessed. Patients with tumors that exhibited LDR to platinum (27 patients) were compared with patients with tumors that exhibited IDR/EDR to platinum (18 patients). In summary, 18 of 27 patients (67%) with LDR are alive; 9 of 18 patients (50%) with IDR/EDR are alive at publication. This study demonstrates a significant flaw because therapy was not chosen or based on assay results. The authors recommended a phase III randomized clinical trial to test whether EDR assay is associated with improved survival compared with empiric chemotherapy.

Another article demonstrates EDR is common after prior exposure to paclitaxel but does not correlate EDR assay results with clinical outcomes (clinical utility).

A prospective study of 43 patients with ovarian cancer received 6-9 cycles of platinum and taxane. PFS and OS among patients with and without EDR to platinum were not clinically significant. The authors recommended a prospective trial to select first- and second-line chemotherapy to define the clinical efficacy of the assay.

More recently, a retrospective review of 377 primary ovarian cancer patients demonstrated EDR assay results do not independently predict or alter the outcomes of patients treated with current standard of primary cytoreductive surgery followed by platinum and taxane combination chemotherapy⁷. Study flaws are discussed in the letters to the editor. However, the authors of the letters to the editor admit a prospective registration trial controlling various factors will be necessary to determine the ability of an *in vitro* assay to truly predict response, time to progression and OS.

Two 2009 retrospective studies provide conflicting insight into the clinical utility of the EDR assay. In the first study EDR was assessed in 253 ovarian cancer patients. Dual-resistance was defined as at least one EDR in the primary and secondary treatment groups. The authors concluded that the presence of EDR to multiple agents was not associated with OS in advanced stage epithelial ovarian, fallopian and primary peritoneal cancers. In the second study 58 of 173 patients who underwent optimal primary cytoreduction with ovarian tumor LDR to both platinum and taxane demonstrated statistically improved PFS and OS compared with the 115 patients who demonstrated IDR or EDR to these agents.

It is noteworthy the 2009 National Comprehensive Cancer Network (NCCN) guidelines noted that *in vitro* CSRAs should not be recommended due to the lack of demonstrable efficacy for choosing a chemotherapy regimen. In 2010 without supporting clinical trials, NCCN notated that CSRAs are used in some NCCN Centers. However, NCCN indicated that the current level of evidence is not sufficient to supplant standard of care chemotherapy.

July 25, 2011, The American Society of Clinical Oncology Clinical Practice Guideline updated the guidelines on the use of CSRA and posted on <http://www.jco.rscopubs.org> ahead of print. "Review of the literature does not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice."

Analysis of Evidence (Rationale for Determination)

Level of Evidence
Quality – Moderate
Strength – Strong
Weight - Moderate

CSRAs are considered investigational and not a covered Medicare benefit.

General Information

Associated Information

This is a non-coverage LCD. Any documentation related to these services should be legible, and maintained in the patient's medical record.

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/01/2019	R4	<p>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)
12/01/2019	R3	<p>12/01/2019: This LCD is being revised in order to adhere to CMS requirements per chapter 13, section 13.5.1 of the Program Integrity Manual, to remove all coding from LCDs. There has been no change in coverage with this LCD revision. Regulations regarding billing and coding were removed from the CMS National Coverage Policy section of this LCD and placed in the related Billing and Coding: In Vitro Chemosensitivity & Chemoresistance Assays A56071 article.</p> <p><i>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in</i></p>	<ul style="list-style-type: none"> Provider Education/Guidance

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		<i>this policy.</i>	
12/01/2019	R2	<p>12/01/2019: At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage.</p> <p>As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.</p>	<ul style="list-style-type: none"> • Provider Education/Guidance • Revisions Due To Code Removal
10/08/2018	R1	<p>The Notice Period Start Date and the Notice Period End Date have been updated to 8/23/18 and 10/07/2018 respectively with a revised Effective Date of 10/08/2018 to coincide with the Response to Comments Effective Date of 10/8/2018. No changes were made to the policy itself.</p> <p>08/14/2018 - At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy. The draft LCD was issued prior to the implementation of the 21st Century Cures Act so the requirement of the Act does not apply to this policy.</p>	<ul style="list-style-type: none"> • Creation of Uniform LCDs Within a MAC Jurisdiction • Other (Change the Notice Period Start and End Dates along with the Effective date.)

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A56071 - Billing and Coding: In Vitro Chemosensitivity & Chemoresistance Assays

A56076 - Response to Comments: In Vitro Chemosensitivity & Chemoresistance Assays

LCD(s)

DL37628

- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

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