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LCD for Oncologic in Vitro Chemoresponse Assays (L22555)

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NHIC, Corp.

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31146

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Carrier

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L22555

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Oncologic in Vitro Chemoresponse Assays

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06-02.5

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

Title XVIII of the Social Security Act, Section 1862 (a)(1)(A), allows coverage and payment for only those services considered medically reasonable and necessary.

Title XVIII of the Social Security Act, Section 1833(e), prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Code of Federal Regulations (CFR), title 42, part 410.32, specifies that all diagnostic tests must be ordered by a provider who is the treating provider for the patient and who will use the test in the patient's care. For laboratory tests, additional documentation of medical necessity may be requested of the referring (treating) provider (Pub. 100-08, Chapter 3.4).

CMS Manual System, Publication 100-08, Program Integrity Manual Chapter 3.4, Additional Documentation Requests. Medicare may request documentation from referring (treating) physicians as part of Medical Review of claims in prepay or postpay settings. This may result in denial of laboratory services as specified here and at 42 CFR 410.32(d).

CMS Manual System, Publication 100-04, Claims Processing Manual, Chapter 16, Section 40.3, Hospital billing under Part A. Hospitals bill Part A for in-house tests and may bill Part A for referred tests to reference laboratories, including tests for inpatients, hospital outpatients, and nonpatients. See also very important rules in Section 120.1 regarding date of service for hospital specimens covered under Part A. Rules for laboratory billing in Part B are superseded by Part A.

CMS Manual System, Publication 100-03, National Coverage Determinations (NCD) Manual, Human Tumor Stem Cell Drug Sensitivity Assays (NCD 190.7; including national coverage analysis, tracking sheets, and related documents).

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HISTORY OF NATIONAL AND LOCAL COVERAGE DECISIONS

National Coverage Decision

Medicare has a National Coverage Decision (NCD 190.7) on human tumor stem cell sensitivity assays which defines two types of assays. (A) Human tumor stem cell drug sensitivity assays involve exposure of human tumor stem cell colonies grown in tissue culture to anticancer drugs and observing for cytotoxic effects. (B) The Fluorescent Cytoprint Assay, a miniaturized organ culture system for cancer chemosensitivity testing, allows for qualitative visual estimation of cell kill using low power microscopy and a noncytotoxic fluorescence probe for cell viability. The NCD states noncoverage for these two tests. Stem cell assays based on colony counts were initially proposed as useful (e.g. Salmon, 1978) but fell sharply from favor (e.g. Selby, 1983; Weisenthal, 1985). Section (B) was added in 1996.

Medicare Coverage Advisory Council and other CMS Guidelines

A Medicare Coverage Advisory Council (MCAC) met in 1999. The Laboratory and Diagnostic Services Panel concluded that clinical response as well as survival rates were appropriate measures of utility and that evidence supported use of the tests with combinations of drugs. The executive committee voted that tumor assay systems should be considered individually. Since certain newer assay systems on which the NCD was silent were already covered by Medicare contractors, no change to the NCD occurred. NHIC, Corp. published articles on coverage and coding in September and in November of 2000. In 2003, CMS reminded contractors that "[The NCD] was very specific to those tests and does not include tumor cell sensitivity or resistance testing on any other class of cells other than tumor stem cells. Contractors have the discretion to determine whether drug response assays on any tumor cell line other than tumor stem cells are reasonable and necessary." CMS specifically instructed contractors not to issue denials "that are routinely appealed and reversed." Administrative Law Judges have very consistently found that certain tumor assay tests meet Medicare's criteria for medical necessity. In 2006, Medicare officially recognized cancer chemosensitivity tests as a special test category in Federal Regulations (42 CFR 414.510(b)(3), 71 FR 69705, 12/1/2006).

American Society of Clinical Oncology (2004)

The American Society of Clinical Oncology (ASCO) published a white paper in 2004 stating 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."* (Schrug et al. 2004, Samson et al., 2004). Therefore, NHIC revisited its coverage position in 2006 by presentation to the Contractor Advisory Committee and consideration of extensive public comment. NHIC reviewed literature after 2003 (e.g. Parker, 2004; Tewari, 2005; Gallion, 2006; Ugerel, 2006). In addition, coverage statements in NHIC's year 2000 articles were converted to the LCD format because reasonable & necessary coverage statements are now placed in LCDs rather than articles.

INDICATIONS

Clinical Summary

The 2004 reviews by Schrag et al. and Samson et al. focused on long-term survival studies, which are limited. There are significant concerns with short-term clinical response (e.g. CT scan) alone, because such responses could, possibly, be unassociated with health outcomes related to morbidity or survival. However, as guidance for Medicare, the MCAC expert panel had previously determined that correlation with clinical response was an appropriate outcome measure, therefore NHIC did not limit review to long-term survival studies. Differing positions on this criterion can cause differing conclusions (read our citation from Markman, 1997). A long-standing finding using the more reliable forms of cell assay is that non-sensitive tumors (resistance or "extreme resistance" assays, for example, cells exposed to superpharmacologic concentrations) do not represent clinical responders. On the other hand, a positive or "sensitive" in vitro response is variably associated with an initial clinical response or non-response. If this principle is accepted, the clinical question is not whether the test is 95% likely to rule in or rule out a single chemotherapy choice, but whether the test removes from clinical consideration certain chemotherapy choices which are a priori reasonable, but likely to be ineffective after test results are considered.

Practice in Clinical Oncology

One standard for Medicare coverage decisions is "general acceptance" in the medical community, while "acceptance by individual health care providers, or even a limited group of health care providers" fails to meet this standard (PIM Chapter 13.7.1). One laboratory under NHIC jurisdiction had hundreds of referring Medicare providers in 2005, requesting over 2,000 assays for ovarian cancer alone (the incidence in the Medicare population is circa 10,000). NHIC must view these referrals as showing a tenable standard of practice and not "an individual provider or small group." See also e.g. Orr (1999), Tewari (2005). However, to NHIC's knowledge there has never been a national organization's guideline that sensitivity testing is required for chemotherapy decisions, and this LCD shall in no way be construed as making any such suggestion. E.g., the NCCN (2006) guidelines for ovarian cancer therapy do not incorporate a step for chemosensitivity testing. Data which could underlie unambiguous guidelines as to which assay formats are best for which tumors or which drugs would be very useful, according to articles and reviews both before and after the 1999 MCAC.

Drugs Tested; Pan-resistant Tumors

It is only reasonable to test drugs which are mechanistically valid in the in vitro setting, e.g. do not depend on an immunoresponse or a response longer than the test period. In some cases an active metabolite is clinically appropriate to test (Parker, 2004). The 1999 MCAC determined that resistance should not preclude use of a given drug (or regimen). For example, certain tumors may test as "pan-resistant," but a form of chemotherapy may still be offered the patient. NHIC notes, however, that it is not reasonable to test drugs and combinations of drugs that are not truly "on the table" for clinical use for a given patient.

The 1980's NCD specifically described "stem cell" colony assays and referred to then-contemporary assays using as agar-implanted cell "colonies." Interest in cancer stem cells has resurged since 2000 (see review and quotation, Jordan et al. 2006). In principle, extensively validated assays unrelated to the 1980s "stem cell colony assays" would not be non-covered by the NCD.

Jurisdiction for Medicare Part A and B

Although not determined by this LCD, providers must be aware that CMS has complex bundling and jurisdiction rules for hospital-origin tissue and lab tests even when completed outside the hospital and after discharge. See excerpt from 42 CFR 414.510 in the *Appendix* section. See the Coding & Billing article attached to this LCD.

LIMITATIONS

Chemosensitivity (resistance) testing is not FDA-approved because it is a locally developed test and not marketed as a kit. Labs and specific tests must meet CLIA and CAP certification

requirements.

Testing which is not empirically validated in relation to clinical response is not covered. For example, a novel testing technique is not automatically assumed to correlate with clinical performance simply because it measures cell survival or death in vitro.

Testing for drugs or regimens not under active consideration for chemotherapy is considered an investigational use of the laboratory service, and is not covered.

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Diagnostic Tests and X-Rays

Coding Information

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Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

0	TBD
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Revenue Codes: [back to top](#)

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

99999	Not Applicable
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Depending on the assay, tests may be billed with a variety of laboratory fee schedule, physician (pathology) fee schedule, or unlisted codes after conferral with the contractor. See the attached coding and billing article.

XX000	Not Applicable
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The most common uses of chemosensitivity (resistance) testing are for ovarian, lung, and gastrointestinal carcinomas and certain hematopoietic tumors. Depending on tissue availability, culture response, and clinical factors other malignancies may be appropriately tested (e.g. gliomas, Parker, 2004). However, an ICD-9-CM list is not provided because the CPT codes used in testing are general laboratory codes for cell culture or special stains and could not be edited against a specific list of cancer ICD-9-CM codes.

XX000 Not Applicable

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ICD-9 Codes that DO NOT Support Medical Necessity [back to top](#)

XX000 Not Applicable

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General Information

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Physician's order for specific tests and tests results should be available upon request.

Negotiated rulemaking for laboratories indicates that upon medical review and determinations of the contractor, payment to the billing laboratory may be denied based on inadequate or nonsupportive documentation of a referring physician (see 42 CFR 410.32(d) and Program Integrity Manual, Chapter 3, Section 3.4.1.2.) By regulation, contractors are allowed to request documentation from the referring physician as part of the medical review.

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Regulations and manual sections determine that Part A jurisdiction and inpatient (DRG) bundling rules may apply to certain hospital-origin specimens, even when the lab test is brought to completion outside the hospital or after the patient is discharged. See 71 FR 69705 (published 12/1/2006, effective 1/1/2007). See also CMS Manual System, Publication 100-04, Claims Processing Manual, Chapter 16, Section 120.1; and Section 40.3, Hospital billing under Part A for lab tests. For outpatients see also Pub.100-02, Benefit Policy Manual, Chapter 6, Section 20.3.3.

42 CFR 414.510 Laboratory date of service for specimens

The date of service for a laboratory test is as follows:

(a) Except as provided under paragraph (b) of this section, the date of service of the test must be the date the specimen was collected. [text omitted]

(b)(3) In the case of a chemotherapy sensitivity test performed on live tissue, the date of service of the test must be the date the test was performed only if

(i) The decision regarding the specific chemotherapeutic agents to test is made at least 14 days after discharge;

(ii) The specimen was collected while the patient was undergoing a hospital surgical procedure;

(iii) It would be medically inappropriate to have collected the sample other than during the hospital procedure for which the patient was admitted;

(iv) The results of the test do not guide treatment provided during the hospital stay; and,

(v) The test was reasonable and medically necessary for the treatment of an illness.

(4) For purposes of this section, "chemotherapy sensitivity test" means a test identified by the Secretary as a test that requires a fresh tissue sample to test the sensitivity of tumor cells to various chemotherapeutic agents. The Secretary identifies such tests through program instructions.

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Gallion H et al. (2006) Progression-free interval in ovarian cancer and predictive value of an ex vivo chemoresponse assay. *Int J Gyn Cancer* 16:194

Jordan C et al. (2006). Cancer stem cells. *NEJM* 355:1253. States in part, "Cells with the properties of stem cells are integral to the development and perpetuation of several forms of human cancer. Eradication of the stem-cell compartment of a tumor also may be essential to achieve stable, long-lasting remission, and even a cure, of cancer. Advances in our knowledge of the properties of stem cells have made specific targeting and eradication of cancer stem cells a topic of considerable interest.... It is becoming evident that a cancer treatment that fails to eliminate cancer stem cells may allow regrowth of the tumor. In cases in which bulk disease is eradicated and chemotherapy is given, only to be followed by a relapse, a plausible explanation is that the cancer stem cells have not been completely destroyed. Therapeutic strategies that specifically target cancer stem cells should eradicate tumors more effectively than current treatments and reduce the risk of relapse and metastasis.... we must understand how therapies that effectively target the bulk of tumor cells fail to eradicate cancer stem cells."

Loizzi V et al (2003) Survival outcomes in patients with recurrent ovarian cancer who were treated with chemoresistance assay-guided chemotherapy. *Am J Obstet Gynecol* 189:1301

Markman M (1997) Letter- *Cancer* 79:1449. In response to the statement, "The extreme drug resistance assay accurately identifies ineffective chemotherapy and helps the oncologist avoid unnecessary treatments and toxicity" Markman wrote, "It is unquestionable that oncologists use these assays to assist in the positive selection of chemotherapeutic agents. Therefore, it is highly

relevant to ask if the use of such an assay improves quality of life, reduces toxicity, improves survival, or reduces cost. In the absence of actual data....it is inappropriate to make claims...." Markman's mismatch between anatomic response or delayed time to progression and survival does occur. For example, in 356 recurrent ovarian cancer patients gemcitabine (Gemzar) extended time to progression ($p < 0.05$) but was not shown to extend survival (Oncology Drugs Advisory Committee Meeting, FDA, 3/13/2006, p.8). By law, when approved by the FDA (7/14/2006) or listed in an approved compendium, such a cancer drug and indication are statutorily covered by Medicare [SSA 1862(t)(2)(B)(i).] For a similar example see Geyer, 2006 NEJM 355:2733, Fig. 2B; Muss, 355:2783. As noted in the body of the LCD, NHIC found that the MCAC had already determined that clinical response per se was an appropriate benchmark for Medicare's review of chemosensitivity assays. NHIC saw no standing to reconsider the conclusions of a national Medicare expert panel. Decision models used by private insurers (e.g. Cigna; Regence Blue Cross) may work from different assumptions and reach different conclusions.

National Cancer Center Network (NCCN, 2006) Updated guidelines for ovarian cancer, 3/6/2006
http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf

Orr JW et al. (1999) Cost-effective treatment of women with advanced ovarian cancer...directed by an in vitro assay by drug resistance. *Cancer J Sci Am* 5:174

Parker et al (2004) A Prospective Blinded Study of the Predictive Value of an Extreme Drug Resistance Assay in Patients Receiving CPT-11 for Recurrent Glioma. *J Neuro-oncol* 66:365

Salmon SE et al (1978) Quantitation of differential sensitivity of tumor stem cells to anti-cancer drugs *NEJM* 298:1321

Samson et al (2004) Chemotherapy Sensitivity and Resistance Assays: A Systematic Review. *J Clin Oncol* 22:3618

Schrag et al (2004) American Society of Clinical Oncology Technology Assessment: Chemotherapy Sensitivity and Resistance Assays. *J Clin Oncol* 22:3631. Verified as an active ASCO technology assessment online (12/20/2006). The Schrag group later added, "Guidelines and technology assessments are not intended to supplant physician judgment...It is certainly each practitioner's prerogative to order CSRA's. However, it is important to specify to the patient what the treatment would be in the absence of the assay and to be clear about if and how the information will be used to inform treatment decision making." *J Clin Oncol* 23:3647.

Selby P (1983) A critical appraisal of the "human tumor stem-cell assay." *NEJM* 308:129

Tewari KS et al (2005) Conservation of in vitro drug resistance patterns in epithelial ovarian carcinoma. *Gyn Oncol* 98:360

Ugerel S et al (2006) In vitro drug sensitivity predicts response and Survival after individualized sensitivity-directed chemotherapy in metastatic melanoma. *Clin Cancer Res* 12:5454

Weisenthal LM, Lippman ME (1985) Clonogenic and non-clonogenic in vitro chemosensitivity assays. *Cancer Treatment Rep* 69:615

Yancik R (1993) Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 71 (2 Supp) 517 About 50% of cases over 65. Other data gives US incidence circa 20,000/year.

Administrative Law Judges have very consistently found that certain tumor assay tests meet Medicare's criteria for medical necessity (for example, guidance in a broadly used American textbook such as DeVita, Principles and Practice of Oncology, 2001).

DeVita DT et al. (2001) *Cancer: Principles and Practice of Oncology*, Lippincott.

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The Local Coverage Determination was presented at the April 19, 2006, Contractor Advisory Committee (CAC) Meeting.

This policy does not reflect the sole opinion of the contractor or Contractor Medical Director. Although the final decision rests with the contractor, this policy was developed in cooperation with advisory groups, which includes representatives from a variety of medical specialty groups.

Medical policies are written based on the available medical scientific literature and current standards of practice. For some policies, there may be unique circumstances that require special consideration. In those circumstances, providers may submit relevant clinical information for payment consideration.

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Added a reference to the Source of Information section.

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Updated on 12/31/2006 with effective dates 02/19/2007 - N/A

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