

Corporate Medical Policy

In Vitro Chemoresistance and Chemosensitivity Assays

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Last CAP Review: 4/2012
Next CAP Review: 4/2013
Last Review: 4/2012

Description of Procedure or Service

In vitro chemoresistance and chemosensitivity assays have been developed to provide information about the characteristics of an individual patient's malignancy to predict potential responsiveness of their cancer to specific drugs. Thus, these assays are sometimes used by oncologists to select treatment regimens for an individual patient. Several assays have been developed that differ with respect to processing of biological samples and detection methods. However, all involve similar principles and they share protocol components including: 1) isolation of cells and establishment in an in vitro medium (sometimes in soft agar); 2) incubation of the cells with various drugs; 3) assessment of cell survival; and 4) interpretation of the result.

A variety of chemosensitivity and chemoresistance assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and non viable cells to quantify cell kill following exposure to a drug of interest. For the Oncotech Extreme Drug Resistance Assay (EDR®; Exiqon Diagnostics, Tustin, CA); and the ChemoFX® assay (Precision Therapeutics; Pittsburgh, PA) premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the tests are performed in a laboratory that licensed by CLIA for high-complexity testing.

With few exceptions, drug doses used in the assays are highly variable depending on tumor type and drug class. But all assays require drug exposures ranging from several-fold below physiological relevance to several-fold above physiological relevance.

Although a variety of assays exist to examine chemosensitivity or chemoresistance, only a few are commercially available and currently used in the clinic periodically.

The DiSC assay uses dye exclusion by live cells

- The Differential Staining Cytotoxicity (DiSC) Assay involves mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation. Cells are then established in culture and treated with the drugs of interest at three dose levels; the middle dose is that which could be achieved in therapy; 10-fold lower than the physiologically relevant dose; and, 10-fold higher. Exposure time ranges from 4-6 days; then, cells are restained with fast green dye and counterstained with hematoxylin and eosin. The fast green dye is taken up by dead cells, and hematoxylin and eosin can differentiate tumor cells from normal cells. The intact cell membrane of a live cell precludes staining with the green dye. Drug sensitivity is measured by the ratio of live cells in the treated samples to the number of live cells in the untreated controls.

Several methods measure incorporation of radioactive precursors by macromolecules in viable cells.

- Tritiated thymine incorporation measures uptake of tritiated thymidine by DNA of viable cells. Using proteases and DNase to disaggregate the tissue, samples are seeded into single cell suspension cultures on soft agar. They are then treated with the drug(s) of interest for four days. After three days, tritiated thymidine is added. After 24 hours of additional incubation cells are

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lysed and radioactivity is quantified and compared to a blank control consisting of cells that were treated with sodium azide. Only cells that are viable and proliferating will take up the radioactive thymidine. Therefore, there is an inverse relationship between uptake of radioactivity and sensitivity of the cells to the agent(s) of interest.

- The Extreme Drug Resistance assay (EDR®) (commercially available at Exiqon Diagnostics, Tustin, CA) is methodologically similar to the thymidine incorporation assay, using metabolic incorporation of tritiated thymidine to measure cell viability; however, single cell suspensions are not required, so the assay simpler to perform. Small tissue samples are incubated with the drug(s) of interest for 5 days at doses ranging from 5-fold below to 80-fold above concentrations that would reflect physiological relevance. Subsequently, tritiated thymidine is added to the culture and uptake is quantified after various incubation times. Only live (resistant) cells will incorporate the compound. Therefore, the level of tritiated thymidine incorporation is directly related to chemoresistance. The interpretation of the results is unique in that resistance to the drugs is evaluated as opposed to evaluation of responsiveness. Tumors are considered to be highly resistant when thymidine incorporation is at least one standard deviation above reference samples.
- The Histoculture Drug Resistance Assay (HDRA) http://www.anticancer.com/HDRA_ref.html is commercially available by AntiCancer, Inc. (San Diego, California) tests tissue fragments 1 to 2 millimeters in size. Samples are placed on a collagen matrix so they can grow 3 dimensionally and maintain signaling pathways mediated by cadherins and integrins, which control cell-cell and cell-matrix contact, respectively. After 24 hours, explants are incubated with drug for 3 days. Subsequently, they are fixed in formalin and embedded in paraffin. Radioactivity is quantified in slide sections using autoradiography.

Drug sensitivity is evaluated by quantification of cell growth in the 3-dimensional collagen matrix. There is an inverse relationship between the drug sensitivity of the tumor and cell growth. Concentrations of drug and incubation times are not standardized and vary depending on drug combination and tumor type.

- The Adenosine Triphosphate (ATP) Bioluminescence Assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, then exposed to drugs. Following incubation with drug the cells are lysed and the cytoplasmic components are solubilized under conditions that will not allow enzymatic metabolism of ATP. Luciferin and firefly luciferase are added to the cell lysis product. This catalyzes the conversion of ATP to adenosine di- and monophosphate and light is emitted proportionally to metabolic activity. This is quantified with a luminometer. From the measurement of light, the number of cells can be calculated. A decrease in ATP indicates drug sensitivity, whereas no loss of ATP suggests that the tumor is resistant to the agent of interest.
- Precision Therapeutics (Pittsburgh, Pennsylvania) commercially markets ChemoFX®, which uses this technology <http://www.chemofx.com/index.html>. While the firefly luciferase and luciferin catalyze reduction of ATP and emitted light is quantified using a luminometer; cells must be grown in a monolayer rather than in a three-dimensional matrix.

The rationale for chemosensitivity assays is strongest where there are a variety of therapeutic options and there are no clear selection criteria for any particular regimen in an individual patient.

*****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 considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions.

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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

1. In vitro chemosensitivity assays, including but not limited to the histoculture drug response assay or a fluorescent cytoprint assay, are considered **investigational**.
2. In vitro chemoresistance assays, including but not limited to extreme drug resistance assays, are considered **investigational**.

Policy Guidelines

There have been no studies published with a randomized, prospective, design to evaluate this testing. Therefore to date, the clinical utility of chemoresistance and chemosensitivity assays has not been determined, and data are insufficient to determine whether use of the test to select chemotherapy regimens for individual patients will improve outcomes. Most studies have been relatively small correlational designs that evaluated the association between assay results and already known patient outcomes; and, most acknowledge that larger studies are needed. Furthermore, unexpected limitations have arisen including sampling bias due to heterogeneity of tumors and, insufficient biospecimen processing resulting in unevaluable data.

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 codes: There are no specific CPT or HCPCS codes for this service.

The extreme drug resistance assay is a multistep laboratory procedure that might be identified by the following CPT codes: 88358, 88305, 88104, 87230, 88313, and/or 89050. Providers may use 89240 for this service.

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.

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Scientific Background and Reference Sources

TEC 12/95

BCBSA Medical Policy Reference Manual 3/96

Medical Policy Advisory Group review 3/99

Specialty Matched Consultant Advisory Panel - 9/2000

Medical Policy Advisory Group - 9/2000

Specialty Matched Consultant Advisory Panel - 6/2002

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 12/17/2003.

Specialty Matched Consultant Advisory Panel - 5/2004

Schrag D, Garewal HS, Burstein HJ, et al. American Society of Clinical Oncology technology assessment: chemotherapy sensitivity and resistance assays. *J Clin Oncol*. 2004; 22(17):3631-8.

BCBSA Medical Policy Reference Manual [Electronic]. 2.03.01, 8/17/2005

Specialty Matched Consultant Advisory Panel - 3/2006

BCBSA Medical Policy Reference Manual [Electronic]. 2.03.01, 2/14/08

Specialty Matched Consultant Advisory Panel - 3/2008

Schrag D, Garewal HS, Burstein HJ et al. American Society of Clinical Oncology technology assessment: chemotherapy sensitivity and resistance assays. *J Clin Oncol* 2004;22(17):3631-8.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 2/14/08.

Senior Medical Director - 4/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 4/24/09

Specialty Matched Consultant Advisory Panel – 5/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 4/8/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 4/14/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.03.01, 3/8/2012

Specialty Matched Consultant Advisory Panel – 4/2012

Policy Implementation/Update Information

8/83 Original policy

11/84 Reaffirmed

11/87 Evaluated: Investigational

2/96 Evaluated: Added NCDR

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- 3/96 Reaffirmed: National Association reviewed 3/96
- 3/97 Reaffirmed
- 3/99 Reviewed, Reaffirmed, Medical Policy Advisory Group.
- 6/99 Reformatted, Medical Term Definitions added.
- 11/99 Archived
- 6/00 Reactivated due to investigational status of assay
- 9/00 Specialty Matched Consultant Advisory Panel review. No recommended changes to criteria. Medical Policy Advisory Group review. No change to criteria. Approve.
- 12/00 Revised description.
- 5/01 Changes in formatting.
- 2/02 Coding format change.
- 6/02 Specialty Matched Consultant Advisory Panel. No changes. Approve.
- 4/04 Benefits Application and Billing/Coding sections updated for consistency.
- 6/10/04 Specialty Matched Consultant Advisory Panel review. No changes to policy. Referenced added. Notification given 6/10/2004. Effective date 8/12/2004.
- 4/10/06 Specialty Matched Consultant Advisory Panel review 3/15/06. Added current terminology, "chemoresistance and chemosensitive assay" where appropriate. Referenced medical policy, "Clinical Trial Services for Life-Threatening Conditions, MED1093" in the "Description" section. Added the following statement to the "Policy" section; "Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions." Rationale added to the "Policy Guidelines" section. References added.
- 6/2/08 Specialty Matched Advisory Panel review 3/17/08. No change to policy statement. Updated the "Policy Guidelines" section. References added.
- 4/27/09 Policy name changed from "Human Tumor Stem Cell Drug Sensitivity Assay" to "In Vitro Chemoresistance and Chemosensitivity Assays". Reviewed with Senior Medical Director 4/7/09. "Description" section revised. "In vitro chemosensitivity assays, including but not limited to the histoculture drug response assay or a fluorescent cytoprint assay, are considered investigational." "In vitro chemoresistance assays, including but not limited to extreme drug resistance assays are considered investigational." Added CPT code 89240 to "Billing/Coding" section. Notice given 4/27/09. Effective date is 8/3/09. (btw)
- 6/22/10 Policy Number(s) removed. (amw)
- 7/6/10 Specialty Matched Consultant Advisory Panel review 5/24/2010. Updated "Description" section. No changes to policy statement. Added the following statement to the "Billing/Coding" section; "The extreme drug resistance assay is a multistep laboratory procedure that might be identified by the following CPT codes: 88358, 88305, 88104, 87230, 88313, and/or 89050. Providers may use 89240 for this service. References added. (btw)
- 5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. "Description" section revised. No other changes to policy statement. Reference added. (btw)
- 6/21/11 Reference added. (btw)
- 5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. Updated Policy Guidelines. No change to policy intent. Reference added. (btw)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.