

American Society of Clinical Oncology Technology Assessment: Chemotherapy Sensitivity and Resistance Assays

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Submitted May 12, 2004; accepted June 3, 2004.

Disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2217-1/\$20.00

DOI: 10.1200/JCO.2004.05.065

A B S T R A C T

Purpose

To develop a technology assessment of chemotherapy sensitivity and resistance assays in order to define the role of these tests in routine oncology practice.

Methods

The American Society of Clinical Oncology (ASCO) established a Working Group to develop the technology assessment. The Working Group collaborated with the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center. The Working Group developed independent criteria for selecting articles for inclusion in the ASCO assessment, and developed a structured data abstraction tool to facilitate review of selected manuscripts. One Working Group member and an ASCO staff member independently reviewed the 1,139 abstracts identified by the BCBSA comprehensive literature search, and by an updated literature search performed by ASCO using the BCBSA search strategy (1966 to January 2004). Of the 12 articles included in this technology assessment, eight were identified by the original BCBSA systematic review, one was provided by industry, and three were identified by the ASCO updated literature review.

Results

Review of the literature does not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice.

Recommendations

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.

J Clin Oncol 22. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Chemotherapy sensitivity and resistance assays (CSRAs) offer the potential of selecting cancer treatments based on responsiveness of individual tumors as measured using *in vitro* assays. Because of the possibility of tailoring treatment to individual patients—using effective agents while sparing unnecessary ones—there is an intrinsic appeal to this notion. A variety of CSRAs have been developed, and some have been studied in clinical trials. The American Society of Clinical Oncology

(ASCO) embarked on a technology assessment of CSRAs in order to define the role of these tests in routine oncology practice.

Definition of CSRAs

A chemotherapy sensitivity assay refers to any *in vitro* laboratory analysis that is performed specifically to evaluate whether tumor growth is inhibited by a known chemotherapy drug or, more commonly, a panel of drugs. Sometimes these assays are referred to as chemoresistance assays because they identify agents that do not influence *in vitro* tumor cell growth. In this

technology assessment, we refer to both types of analyses as CSRAs. They are contrasted with empiric therapy, which refers to choice of chemotherapy based on the clinical literature describing outcomes achieved when patients receive particular chemotherapy agents. This technology assessment summarizes the evidence on the use of CSRAs and offers recommendations for clinical practice regarding the utility of this technology. This review focuses exclusively on CSRAs performed on viable patient tumor tissue. These assays contrast with strategies such as immunohistochemistry, single gene expression, and transcript profiling, which are performed on nonviable patient tumor tissue and may also yield information predicting the likelihood of response to particular drugs. The best-known example in this latter category is HER-2 overexpression and trastuzumab response in patients with advanced breast cancer.

Technology Assessment Process

ASCO defines a technology assessment as a process for determining whether a procedure is appropriate for broad-based conventional use in clinical practice. The process used in this technology assessment followed defined ASCO policies and procedures. The topic of chemotherapy sensitivity and resistance assays was nominated and approved by the ASCO Health Services Committee (HSC), and subsequently approved by the ASCO Board of Directors.

Literature Review and Analysis

The HSC learned that the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) had conducted a systematic review on this exact topic under contract to the Health Care Financing Administration. The HSC negotiated a collaborative relationship with BCBSA through which ASCO was granted access to the systematic review for use in the technology assessment development process. The Working Group convened in Chicago in June 2001, with representatives from the BCBSA TEC, to discuss the systematic review and to formulate a process for developing recommendations. The ASCO Working Group decided to use the BCBSA systematic review analysis as a template, but agreed to review the methods used, to identify additional relevant sources of information, and to review independently the articles selected for inclusion in the BCBSA systematic review. The BCBSA systematic review is published in this issue of the *Journal of Clinical Oncology*.¹

The Working Group developed independent criteria for selecting articles for inclusion in the ASCO assessment. To be included, a study had to compare outcomes for patients whose chemotherapy was chosen empirically (based on the clinical trial literature) versus patients for whom chemotherapy was chosen based on the results of CSRAs. Studies did not have to randomly assign patients to assay-guided or empiric therapy, but had to include a total of 20 or more patients per group. We excluded reports that only reported correlations between assay results and clinical

outcomes. Numerous analyses were retrospective evaluations of whether assay results predicted clinical outcomes. Retrospective analyses were included, provided that assay results were used to assign treatment for a group of 20 or more patients.

One Working Group member (D.S.) and an ASCO staff member (M.R.S.) independently reviewed the 1,139 abstracts identified by the BCBSA comprehensive literature search, and by an updated literature search performed by ASCO using the BCBSA search strategy (1966 to January 2004). Seventeen abstracts met inclusion criteria. The full text of each of these articles was reviewed by a steering committee of the Working Group, and 11 articles were ultimately selected as meeting the inclusion criteria. These 11 include two reports not previously identified in the BCBSA review.

In order to identify additional articles regarding CSRAs, the Working Group contacted firms that market these products commercially and requested relevant literature. An additional 20 abstracts or articles were provided by these firms and reviewed by two members of the Working Group. One of these studies met inclusion criteria. Thus, in summary, of the 12 articles included in this technology assessment, eight were identified by the original BCBSA systematic review,²⁻⁹ one was provided by industry,¹⁰ and three were identified by the ASCO updated literature review.¹¹⁻¹³ These same 12 studies are the subject of the BCBSA systematic review.

The Working Group developed a structured data abstraction tool to facilitate review of selected manuscripts. Three Working Group members (H.J.B., H.S.G., and D.S.) independently extracted data from each manuscript to create summary evidence tables. These were circulated to the Working Group for use in developing recommendations and consensus on the final manuscript.

Working Group Selection and Composition

The HSC convened a Working Group that included individuals with expertise in laboratory and clinical aspects of chemotherapy sensitivity and resistance assay development, clinical trial methodology, and guideline development. As per ASCO policies and procedures, the Working Group included core members from the HSC, ad hoc members with content expertise in the area of CSRAs, and a patient representative. One BCBSA representative (D.J.S.) served on the Working Group in an ex-officio capacity (see Appendix for a list of Working Group members and institutional affiliations).

Disclosure of Conflict of Interest

All Working Group members complied with ASCO policy on conflict of interest, which requires disclosure of any interest (financial or otherwise) that might be construed as constituting an actual, potential, or apparent conflict. Members completed ASCO's disclosure form and were asked at the face-to-face meeting to report ties to companies

developing products that might be affected by promulgation of the technology assessment report. Information was requested regarding employment, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. One member of the original Working Group chose to resign based on a self-identified perceived conflict. No other limiting conflicts were identified among the Working Group members.

CSRAs

Table 1 describes technical aspects of the CSRAs used in trials identified by the literature review. Table 2 summarizes the study design and findings from each study. These assays and the studies evaluating their performance are described in much greater detail in the BCBSA systematic review. The key features are summarized here in abridged format to provide practitioners with an overview of this challenging literature.

Interpretation of Literature on CSRAs

All clinical oncologists desire a strategy to use customized information to make chemotherapy recommendations that are tailored specifically to a patient's tumor characteristics. The approach has enormous intuitive appeal and is more logical to both patients and physicians than the empiric approach, whereby all patients with similar tumor type are treated according to a standardized regimen. However, obstacles will remain before CSRAs are integrated into general clinical care. To date, the available literature on CSRAs does not support use of this technology outside of a clinical research trial.

Limitations in the literature include small sample sizes, the lack of prospective studies, the generally low yield of assays, and the availability of newer chemotherapy and biologic agents since the advent of these trials. When interpreting the literature on this technology, clinicians should bear in mind the following considerations:

(1) *How often does the assay yield clinically useful results? Is there a clear definition of what constitutes a successful assay?* For technically challenging assays requiring colony formation, such as the human tumor cloning assay and surgical procedures including the subrenal capsule assay, the success rate of the procedure is modest, despite varying definitions of success. Moreover, preparation of the assay may involve complex laboratory work. This limits the ability to export this technology to nonresearch settings, and limits broad application of the technology to routine clinical practice. Assays that do not require cell culture have a theoretic advantage in that a larger fraction of specimens may yield interpretable results. Nevertheless, interpretation of these results may be compromised by the lack of a reference standard or clear cutoff to distinguish chemotherapy sensitivity from resistance, and difficulty related to standardization and reproducibility of laboratory technique. Assay results may take several weeks to analyze given the need for successful cell culture. This may pose a problem when there is a clinical basis for more rapid initiation of therapy.

A successful CSRA should have a high yield and provide interpretable results for the majority of patients whose tumor tissue undergoes analysis. Results should also be

Table 1. Overview of the Chemotherapy Sensitivity and Resistance Assays Represented in the Technology Assessment

Assay Name	Target Tumor Types*	Assay Description
SRCA ¹²	Epithelial ovarian cancers	Human tumor specimens are cultured in the subrenal capsule of mice. Tumor growth in mice is measured following treatment with various drugs or saline to determine drug sensitivity.
HTCA and CCS ^{6,8}	Multiple tumor types	Single cell suspensions prepared from patients' tumors are cultured in vitro for several weeks. The colony-forming efficiency of these cells in the presence and absence of various drugs is evaluated to determine drug sensitivity.
DiSC ^{3,5,6,9}	Lung cancer (small and non-small-cell)	Tumor cells are cultured in vitro in the presence/absence of three concentrations of drug. After a 6-day incubation, differential dye staining is used to identify viable cells and determine drug sensitivity.
MTT ¹⁰	Breast cancer	Tumor cell suspensions are cultured with various chemotherapy agents for 4 days. MTT is then added; because it reduces intracellularly to a blue dye, the intensity of uptake yields an estimate of the number of viable cells to determine drug sensitivity.
ATP ¹¹	Epithelial ovarian cancer	Tumor cells are cultured in the presence/absence of test drugs and then cells are lysed. The amount of ATP—a reflection of the number of viable cells—is measured by adding luciferin (the same compound which causes fireflies to glow). Low ATP concentration manifests as low luminescence to identify efficacious test drugs.
EDR assay ^{14,15}	Epithelial ovarian cancer	After successful culture, tumor cells obtained from fresh biopsy specimens are labeled with tritiated thymidine. The level of uptake is tracked after exposure to chemotherapy concentrations that approximate the peak level achieved clinically. Extreme resistance is identified when thymidine incorporation is inhibited in the presence of the drug by less than one standard deviation of the median cell inhibition measured for several hundred reference tumor samples.

Abbreviations: SRCA, subrenal capsule assay; HTCA, human tumor cloning assay; CCS, capillary cloning system; DiSC, differential staining toxicity; MTT, methyl thiazolyl-diphenyl-tetrazolium bromide; ATP, adenosine triphosphate bioluminescence; EDR, extreme drug resistance assay.

*The target tumor types indicated in the table refer to the patients included in the 12 research studies that met Working Group inclusion criteria. Most assays have potential relevance to multiple tumor types.

Table 2. Summary of Studies Evaluating the Clinical Utility of Chemotherapy Sensitivity and Resistance Assays

Study and Assay	Design	Proportion of Patients With Assessable Assays*	Summary of Main Findings† (tumor response rates reported)
HTCA ⁶ (Von Hoff, 1983)	Comparison of the rate of complete and partial responses to chemotherapy for patients with metastatic cancer (multiple sites/histologies) for three non-randomly assigned groups: Group 1: Successful tumor cell culture and assay-guided therapy. Group 2: Cells not successfully cultured, empiric therapy. Group 3: Successful cell culture but empiric therapy delivered because patient refused assay-guided therapy or contraindication to assay recommended agent.	64% (303 of 470 patients) assessable; however, the unit of analysis was the number of assay trials and not the multiple assays performed per patient.	Assay-guided (group 1): 62 of 246; 25% Empiric (group 2): 39 of 256; 14% Empiric (group 3): 11 of 102; 11% Study weakness: the non-random treatment assignment, and that tumor cells could not be assayed in many circumstances because they did not grow in culture.
HTCA ⁸ (Von Hoff, 1991)	Patients with metastatic tumors (sites/histologies) whose HTCA assays identified a chemoresponsive agent were treated with that drug. In vivo complete and partial responses to treatment were measured: Group 1: Eighteen patients received HTCA-guided therapy. These patients were derived from cohort of 75 patients with assessable assays, 31 of 75 of whom had sensitive assays. Group 2: Ninety patients received empiric therapy and had tumor response evaluated. These patients had no assay growth or insensitive assay results.	45% (75 of 168 patients) assessable	Assay-guided (group 1): Five of 18; 28% Empiric (group 2): 10 of 90; 11% Study weakness: the non-random treatment assignment and the inclusion of patients with assay-predicted unresponsive tumors in the comparison group, which comprises interpretability. The analysis did not directly compare assay versus non-assay-guided therapy.
CCS ⁷ (Von Hoff, 1990)	Randomized controlled trial: Group 1: Sixty-eight patients received assay-guided therapy; 19 patients assessable for response in assay-guided group. Group 2: Sixty-five patients received clinician's choice of therapy; 36 patients were assessable for response.	71% (48 of 68 patients) assessable	Assay-guided (group 1): Four of 19; 21% partial response Empiric (group 2): One of 36; 3% partial response There was a higher response rate for drug selection based on CCS than by physician choice, but no survival difference. The strength of this study is the randomization; a weakness is that only a small proportion of patients actually received therapy according to randomization, as well as a lack of complete response data from either group.
DiSC ³ (Gazdar, 1990)	Comparison of response to second-line chemotherapy for small-cell lung cancer for two non-randomly-assigned groups: Group 1: Assay-guided. Successful DiSC assay (n = 26); assay-guided therapy (n = 16). Group 2: Empiric. Unsuccessful assay (n = 53); empiric regimen of vincristine, doxorubicin, and cyclophosphamide (n = 43).	33% (26 of 79 patients) assessable	Assay-guided (group 1): Four of 16; 25% Empiric (group 2): Three of 43; 7% Study weakness: not all patients with successful DiSC assay received assay-guided therapy, and a high proportion of patients lacking assay results received assigned regimen.
DiSC ⁹ (Wilbur, 1992)	No randomization to assay-guided therapy. The DiSC assay was used to measure cell kill in the tumor cell population among a non-consecutively ascertained prospective cohort of 45 patients with advanced NSCLC. Treatment with the three best drugs selected by the assay was administered to 25 of the 35 patients who had a successful assay.	78% (35 of 45 patients) assessable	Assay-guided: Nine of 25; 36% Empiric: not reported Response rate among 12 patients for whom the assay indicated that tumor cells were sensitive to chemotherapy was higher (six of 12; 50%) than response rate among 13 patients for whom assay indicated resistance (three of 13; 23%). Results were similar irrespective of the cutoff point used to define sensitive/resistant. Main study weakness: no comparison between assay-guided and empiric therapy made.

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Chemotherapy Sensitivity and Resistance Assays

Table 2. Summary of Studies Evaluating the Clinical Utility of Chemotherapy Sensitivity and Resistance Assays (continued)

Study and Assay	Design	Proportion of Patients With Assessable Assays*	Summary of Main Findings† (tumor response rates reported)
Modified version of DiSC termed Drug Sensitivity Testing ^{4,5} (Shaw, 1993, 1996)	No randomization to assay-guided therapy. A prospective cohort of extensive stage SCLC patients had DiSC performed on cell lines established after pre-treatment biopsy. All patients received 12 weeks of standard therapy (VP16/ CDDP). For those who had successful cell lines established and did not experience a complete response to VP16/CDDP, therapy during weeks 13-24 was determined by the results of DiSC. A similar study was performed for an analogous cohort of NSCLC patients undergoing biopsy.	Cohort 1: SCLC 29% (33 of 115 patients) assessable Cohort 2: NSCLC 36% (36 of 165 patients) assessable	SCLC (cohort 1): Assay-guided: Five of 21; 24% Empiric: Five of 68; 7% NSCLC (cohort 2): Assay-guided: Two of 21; 9% Empiric: 10 of 69; 14% Study weakness: the non-random treatment assignment, and that a high proportion of tumor cells could not be assayed because they did not grow in culture.
MTT ¹⁰ (Xu, 1999)	Non-randomized prospective study of 156 women with metastatic breast cancer	88% (73 of 83 patients) assessable	Assay-guided: 56 of 73; 77% Empiric: 32 of 83; 39% No difference in either median response or median survival
DiSC ² (Cortazar, 1997)	No randomization to assay-guided therapy. A prospective cohort of extensive stage SCLC had DiSC performed on cell lines established after pre-treatment biopsy and after initial therapy with VP-16/CDDP. The DiSC was used to guide the second 12 weeks of chemotherapy similar to the design by Shaw. Assay-guided therapy was administered when DiSC was successful and when DiSC results were unavailable, empiric therapy with VAC was given.	56% (10 of 18 patients) assessable	Assay-guided: Eight of eight; 100% Empiric: 44 of 44; 100% Superb response rates in both groups Better survival in assay-guided group but incomplete information available about multiple factors influencing selection
ATP ¹¹ (Kurbacher, 1998)	No randomization to assay-guided therapy. A prospective cohort of women with recurrent ovarian cancer had assay-guided therapy if the ATP was successfully performed and the primary physician agreed to abide by the treatment assignment (or alternatively, with empiric therapy).	93% (29 of 31 patients) assessable	Assay-guided: 16 of 25; 64% Empiric: 11 of 30; 37% There were major differences in the treatment regimens selected between two groups. Whereas 23 of 25 patients receiving assay-guided therapy had combination regimens, 21 of 30 receiving empiric therapy had combination regimens. Twelve patients in the assay-guided arm received paclitaxel on a protocol, whereas none of the empiric therapy group received a taxane.
EDR ¹³ (Loizzi, 2003)	No randomization to assay-guided therapy. Retrospective analysis of 50 women with recurrent ovarian cancer treated with assay guidance and 50 women with recurrent ovarian cancer treated empirically.	100% (50 of 50 patients) assessable	Assay-guided: 28 of 50; 56% Empiric therapy: 14 of 50; 28% Platinum-resistant or -sensitive disease was defined based on whether interval from last treatment to progression was more or less than 6 months. Difference between assay and empiric group was greatest for the subset with platinum-sensitive disease. Although there was a statistically significant difference in survival, the authors acknowledged that the study was not designed to determine a statistical difference between assay-guided and empiric therapy groups. They note that the survival analysis was conducted for exploratory, hypothesis-generating purpose only.

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available within a time frame that permits choice of the “in vitro best regimen” versus standard empiric therapy. The cutoffs used to distinguish resistance from sensitivity should be consistent and easily determinable.

(2) *Do assay results depend on the particular lesion biopsied?*
In most analyses, variability of assay results across different biopsy sites is not evaluated. A particular assay may be performed more than once, but generally the same tumor

Table 2. Summary of Studies Evaluating the Clinical Utility of Chemotherapy Sensitivity and Resistance Assays (continued)

Study and Assay	Design	Proportion of Patients With Assessable Assays*	Summary of Main Findings† (tumor response rates reported)
SRCA ¹² (Maenpaa, 1995)	Prospective randomized trial: Group 1: Ninety-eight patients with epithelial ovarian cancer (stage II-IV) assigned to assay-guided therapy (various combination regimens). Group 2: Ninety-eight patients with epithelial ovarian cancer (stage II-IV) assigned to empiric therapy (CAP).	70% (69 of 98 patients) assessable	Assay-guided: 39 of 63; 62% Empiric therapy: 41 of 69; 59% No survival benefit observed. 24 of 63 (38%) patients in assay-guided group received empiric-group therapy of CAP. High number of dropouts.

Abbreviations: HTCA, human tumor cloning assay; CCS, capillary cloning system; DiSC, differential staining cytotoxicity; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; VP16, etoposide; CDDP, cisplatin; MTT, methylthiazolyl-diphenyl-tetrazolium bromide; VAC, vincristine, doxorubicin, and cyclophosphamide; ATP, adenosine triphosphate bioluminescence; EDR, extreme drug resistance assay; SRCA, subrenal capsule assay; CAP, cyclophosphamide, doxorubicin, and cisplatin.

*Sample size refers to the number of assessable patients. For most chemosensitivity and resistance assays, the number of tumor specimens for which assays were initiated greatly exceeded the number ultimately evaluated because of difficulty isolating and preparing tumor cells for in vitro analysis.

†Tumor response rates reported in the table were assessed based on complete plus partial responses.

cell suspension is used each time. Sampling tumor from multiple sites, for example, should yield a similar chemotherapy sensitivity and resistance profile. This is an important, but seldom addressed, control for reliability of the assay results. Development of successful chemotherapy sensitivity and resistance assays will require determination of how assay results vary across different disease sites (eg, primary tumor versus visceral metastasis) obtained from a single patient. It is also not clear if CSRAs built on tissue obtained early in the tumor's history correspond to results that might be obtained downstream with relapse and sequential treatments. Finally, it should be stated that, for patients to have a CSRA performed, they must have tumors that can be obtained via biopsy, paracentesis, or other methods. This could lead to selection biases in the studies reviewed here. For example, patients in the studies would be more likely to have a greater tumor burden and thus a poorer prognosis.

(3) *Does assay-guided therapy affect the choice of chemotherapy agent?* An important clinical parameter that clinicians seek in published reports is an assessment of how often performance of the assay makes a difference for the patient. Difference might be manifest in terms of selection of a particular chemotherapeutic agent or combination, rejection of the treatment which might otherwise have been used if assay results were unavailable, a decision not to treat if the tumor comes back resistant to a number of agents, a decision to pursue treatment if the tumor comes back surprisingly sensitive compared to what might have been expected from the clinical setting, and so on. This type of information, however, is unavailable in the published literature on CSRAs and is not easily obtained.

Often, the chemotherapy combination that looks most promising on the basis of the CSRA is the very same one that would have been chosen in the absence of assay results. This is particularly evident in the analyses of small-cell lung

cancer, where both assay-guided and empiric treatment strategies have typically recommended etoposide and cisplatin. If the assay rarely alters the recommended treatment strategy, the impact of assay results on clinical decision-making can only be minor. CSRAs can only add value if they distinguish between one of several treatment options. If their results consistently serve to validate the use of the same set of drugs that would be selected on the basis of the clinical trial literature, their utility is limited.

Summary of Literature and Recommendations for Practice

The Working Group's review of the literature found that little has changed since the review published by Cortazar and Johnson in 1999.¹⁶ The concept underlying CSRAs remains a compelling one. Unfortunately, there does not appear to be a single assay that is ready for routine integration into the clinical setting. The absence of a suitable CSRA for routine clinical use reflects problems in the technical success and yield of the assays, the lack of adequate prospective evaluation of CSRAs in clinical trials, and the tendency of CSRAs to recommend treatments that would be given empirically.

The single study of a resistance assay that met the Working Group's inclusion criteria deserves special mention. The Loizzi et al¹³ study was designed to compare response rates to chemotherapy for recurrent ovarian cancer among patients receiving either assay-guided therapy or empiric treatment. This was a prospective, but not randomized, clinical trial including 100 consecutive patients (50 treated by assay-guided regimen; 50 empirically). A subset analysis looking at secondary end points among the platinum-sensitive group revealed a survival difference; no survival difference was seen in the platinum-resistant group. Because standard treatment for recurrent ovarian cancer includes platinum therapy, and owing to the lack of

a randomized design and the small number of patients, this study has not made an impact on current treatment recommendations. In addition, the chemotherapy regimens selected under assay-guidance are nearly identical to those selected by empiric treatment. This makes it hard to understand the dramatic difference in survival. It is a provocative finding, which may justify large, randomized, prospective clinical trials with similar treatment elements.

Paradoxically, although there is not yet any compelling evidence that CSRAs should be integrated into routine oncology care, the rationale for their development has increased. When few chemotherapeutic options are available and the array of choices is limited, the potential impact of CSRAs is also circumscribed. Over the past decade, a large number of new therapeutic agents (eg, oxaliplatin, irinotecan, multiple monoclonal antibodies) have been US Food and Drug Administration approved and the array of choices facing oncologists has grown ever more complex. The increasing number of choices makes the rational basis for developing CSRAs even more compelling. This is particularly true for those advanced malignancies with short median survival. A review of several large clinical trials demonstrates that, in the absence of CSRAs, the clinical efficacy of different chemotherapy regimens is very similar.¹⁷ For diseases with short median survival, patients often do not maintain the functional status necessary to receive more than one chemotherapeutic regimen and thus selecting the regimen with the greatest chance of inducing a response is indeed an important goal.

Although the Working Group finds no circumstance in which chemotherapy sensitivity and resistance assays should be obtained to make treatment recommendations in routine clinical practice, this view should not be misconstrued to suggest that this strategy lacks opportunity for further research, particularly with newer therapies. As laboratory techniques become more automated and high throughput analyses become easier to obtain and interpret, better assays will be developed. The *in vitro* approach to determining drug sensitivity and resistance continues to have great potential to spare patients the morbidity of ineffective chemotherapy regimens. Evaluation of these technologies within the context of appropriate research studies should be strongly encouraged within the oncology community.

Thus, based on the evidence from studies that compared outcomes for patients treated with empiric chemotherapy to those treated using assay-guided chemotherapy, 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. Selection of chemo-

therapeutic agents on the basis of results of CSRAs is not warranted based on the current body of evidence. Because the *in vitro* analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.

Recommendations for Future Research

In order to traverse the gulf between the laboratory and the clinic, pilot studies of CSRAs need to establish that the laboratory techniques are technically feasible, yield interpretable results in a high proportion of patients within a time frame adequate for influencing clinical decision-making, and result in treatment recommendations that differ from standard clinical algorithms. Once a CSRA meets these criteria, prospective clinical trials to evaluate clinical efficacy are necessary. These studies should randomly assign patients to the regimens identified on the basis of *in vitro* testing (the "in vitro best regimen"), or to empiric therapy with the standard regimen based on clinical trial data. The end points in these clinical trials should include survival as the clinical measure of outcome. Trials analyzing response rate and/or time to progression might also be informative, but less definitive. In addition, it would be important to discuss any planned clinical study design(s) with regulatory agencies before beginning the studies. This would assure that if the studies demonstrated positive results, they could be used for regulatory approval for wide scale use of a particular CSRA. Unfortunately, the Working Group is not aware of any ongoing or planned studies that include the design elements outlined here.

Finally, it must be acknowledged that the available technology for predicting tumor response to chemotherapy and targeted biologic agents has developed dramatically in the decades since the first efforts to use CSRAs. Trials that take advantage of bioinformatic technologies (eg, gene microarrays) now stand as a viable competing strategy for selecting treatments based on features of tumor biology, and should ideally be conducted alongside traditional *in vitro* sensitivity assays.

Acknowledgment

The Working Group wishes to express its gratitude to Drs Jose Baselga, Patricia Cortazar, David S. Mendelson, Charles W. Penley, John M. Rainey, Robert L. Ruxer, and Antonio C. Wolff for their thoughtful reviews of earlier versions of this technology assessment. Special thanks to Dr David G. Pfister who established the Working Group to address this topic during his tenure as Chair of the ASCO Health Services Committee. Finally, thanks to Jerome Seidenfeld and the Blue Cross and Blue Shield Association Technology Evaluation Center for their collaboration.

Disclosures of Potential Conflicts of Interest

The following contributors have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Axel Hanauske, Eli Lilly & Co, Hoffman-La Roche, iOnGen; Rowan T. Chlebowski, AstraZeneca, Novartis, Aventis, Eli

Lilly & Co. Performed contract work within the last 2 years: Axel Hanauske, Eli Lilly & Co, Hoffman-La Roche. Served as an officer or member of the Board of a company: Anne Hamburger, Biocell, Analytical Biosystems Corp. Received more than \$2,000 a year from a company for either of the last 2 years: Axel Hanauske, Eli Lilly & Co; Jaffer Ajani, Novartis, Aventis, Sanofi, Taiho; Rowan T. Chlebowski, AstraZeneca, Novartis, Aventis, Eli Lilly & Co.

Appendix

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