Correlation of Drug-induced Apoptosis Assay Results With Oncologist Treatment Decisions and Patient Response and Survival

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BACKGROUND: An observational prospective nonblinded clinical trial was performed to determine the effect of a drug-induced apoptosis assay results on treatments planned by oncologists. METHODS: Purified cancer cells from patient biopsies were placed into the MiCK (Microculture Kinetic) assay, a short-term culture, which determined the effects of single drugs or combinations of drugs on tumor cell apoptosis. An oncologist received the assay results before finalizing the treatment plan. Use of the MiCK assay was evaluated and correlated with patient outcomes. RESULTS: Forty-four patients with successful MiCK assays from breast cancer (n = 16), non-small cell lung cancer (n = 6), non-Hodgkin lymphoma (n = 4), and others were evaluated. Four patients received adjuvant chemotherapy after MiCK, and 40 received palliative chemotherapy with a median line of therapy of 2. Oncologists used the MiCK assay to determine chemotherapy (users) in 28 (64%) and did not (nonusers) in 16 patients (36%). In users receiving palliative chemotherapy, complete plus partial response rate was 44%, compared with 6.7% in nonusers (P < .02). The median overall survival was 10.1 months in users versus 4.1 months in nonusers (P = .02). Relapse-free interval was 8.6 months in users versus 4.0 months in nonusers (P < .01). CONCLUSIONS: MiCK assay results are frequently used by oncologists. Outcomes appear to be statistically superior when oncologists use chemotherapy based on MiCK assay results compared with when they do not use the assay results. When available to oncologists, MiCK assay results help to determine patient treatment plans. Cancer 2012;118:4877-83. © 2012 American Cancer Society.

KEYWORDS: chemosensitivity, apoptosis, breast cancer, drug assay, survival, response rate, relapse-free interval, clinical utility.

INTRODUCTION

Physicians have increased the use of predictive bioassays in cancer patients to personalize therapy and improve outcomes. Although prior chemoresistance assays have been developed to try to individualize the choice of cytotoxic chemotherapy, their application has been of limited usefulness. Despite this, some institutions are using these tests in patients, although guidelines have not recommended such testing.

A novel drug-induced apoptosis assay, the MiCK (Microculture Kinetic) assay, has been developed and tested with success in acute myelocytic leukemia. The basis of this assay is the ability of a drug to rapidly induce apoptosis in cancer cells in short-term culture (48 hours) without a need for tumor cell growth. In addition to testing in acute myelocytic leukemia, it has been undergoing testing in solid tumors, including breast cancer, endometrial cancer, lung cancer, miscellaneous solid tumors, and hematologic malignancies.

A large validation study has been completed (Salom et al, unpublished data). These results, presented at the American Society of Clinical Oncology in 2010, indicated a correlation between the use of the best chemotherapy based on the MiCK assay and patient outcomes. Use of the chemotherapy that was best in the MiCK assay produced longer survival and longer relapse-free intervals. Furthermore, physician use of chemotherapy that had significant apoptosis in the MiCK assay produced higher response rates.

This initial observational nonrandomized, multi-institutional prospective trial was conducted to determine how often physicians would use the results of the MiCK assay when the physicians knew the results of the assay before planning and initiating chemotherapy.

MATERIALS AND METHODS

It is of note that >10 years elapsed between initial development of the assay and initiation of this trial. This was because of acquisition of the technology by DiaTech Oncology from Vanderbilt University, and moving the laboratory to the McGill
University campus in Montreal, Canada. Quality control standards were implemented in Montreal, and the laboratory was approved by College of American Pathologists and Clinical Laboratory Improvement Amendments before initiation of the trial.

Patients with cancer of any stage, primary or recurrent, were eligible. Sterile tumor specimens with as much as 1.0 cm³ of viable tumor tissue, 1000 mL of malignant effusions, or 5 mL of leukemic bone marrow aspirate were placed in sterile RPMI, and sent via overnight delivery on cool packs to the DiaTech Oncology laboratory in Montreal.

**Tumor Cell Purification**
Within 24 to 48 hours of collection, the specimen was minced, digested with 0.25 % trypsin and 0.08% DNase for 1 to 2 hours at 37°C, and then filtered through a 100-μm cell strainer. When necessary, nonviable cells were removed by density gradient centrifugation. The cell suspension was then incubated for 30 minutes at 37°C in a tissue culture flask to remove macrophages by adherence. For epithelial tumors, lymphocytes were removed by 30-minute incubation with CD2 antibody-conjugated magnetic beads for T lymphocytes and CD19 antibody-conjugated magnetic beads for B lymphocytes. Remaining macrophages were removed, if necessary, using CD14 antibody-conjugated magnetic beads. The final cell suspension was plated into a 96-well half-area plate, with one 120-μL aliquot per well. The plate was incubated overnight at 37°C with 5% carbon dioxide humidified atmosphere. To give adequate well-bottom coverage, 5 x 10⁴ to 1.5 x 10⁵ cells were seeded per well, depending on the cell volume.

Human JURL-MK2 chronic leukemia in a blast crisis cell line (DSMZ, Braunschweig, Germany) was used as a positive control for MiCK assays performed with patient tumor cells. RPMI-1640 medium without phenol red was used for all cultures. It was supplemented with 10% fetal bovine serum, 100 U/mL of penicillin, and 100 μg/mL of streptomycin. Cell counts and viability were evaluated by trypan blue dye exclusion.

Each tumor cell preparation, after purification of contaminating and necrotic cells, was analyzed by a pathologist using hematoxylin/eosin-stained cytospin preparations to confirm the presence of malignancy cytologically. If an adequate number of cells were available, immunocytochemical stains were also performed to better characterize the tumor phenotype. All specimens achieved at least 90% pure tumor cell content by visual estimation by an experienced pathologist and 90% viability by trypan blue exclusion.

**MiCK Assay for Apoptosis**
The MiCK assay procedure was adapted from the method described previously.³ After overnight incubation, chemotherapy drugs were added to the wells of the 96-well plate in 5-μL aliquots. The number of drugs or drug combinations and the number of concentrations tested depended on the number of viable malignant cells that were isolated from the tumor specimen. The drug concentrations, determined by molarity, were those indicated by the manufacturer as the desired blood level concentration ±1 serial dilution if enough cells were available. After drug addition, the plate was incubated for 30 minutes at 37°C into a 5% carbon dioxide humidified atmosphere incubator. Each well was then overlaid with sterile mineral oil, and the plate was placed into the incubator chamber of a microplate spectrophotometric reader (BioTek, Winooski, Vt). The optical density at 600 nanometers was read and recorded every 5 minutes over a period of 48 hours. Optical density increases, which correlate with apoptosis, were converted to kinetic units (KU) of apoptosis by the proprietary software ProApo with a formula described previously³ and were correlated with patient outcomes. Active apoptosis was indicated as >1.0 KU. A drug producing ≤1 KU was described as inactive, or it was determined that the tumor was resistant to that drug based on previous laboratory correlations of KU with other markers of drug-induced cytotoxicity (growth in culture, thymidine uptake).

**Treatment of Patients**
This study was a prospective multi-institutional non-blinded trial. MiCK assay results obtained before any therapy was initiated were always transmitted to physicians. Physicians treated patients with the physicians’ own choice of drugs as they deemed clinically indicated and were free to use or not use any of the data from the MiCK assay. Tumor responses were measured by Response Evaluation Criteria in Solid Tumors. Patients were evaluated for time to recurrence after assay and survival after assay.

There were no rules or directions regarding how to use the MiCK assay results. The study evaluated whether the oncologist used the results of the assay, other data were also used (eg, estrogen receptor analysis or human epidermal growth receptor 2 [HER2] test results, or addition of other drugs), or the assay results were not used. Because instructions or rules regarding using the assay were not given, it was felt that this was a more valid test of how the assay would be used in actual practice, where oncologist have complete discretion in treatment planning.
Statistical Evaluation
The primary goals of the study were to identify how frequently physicians used the MiCK assay results to help determine patient treatment, and to correlate use of the MiCK assay with response rate, relapse-free interval, and overall survival. Physicians completed questionnaires in which they described what the intended treatment was before the assay data were returned, what treatment was used after the assay was reported, and whether the assay was used in formulating the final treatment given to the patient. Data were imported into SAS software (SAS Institute, Cary, NC) for analysis. If a sample had multiple doses of the same drug, then the concentration with the highest KU value was assigned to the drug. Nonparametric Kaplan-Meier product limit methods were used for survival analysis and the analysis of relapse-free interval. In this analysis, the log-rank test was used to compare survival curves and the Wilcoxon test for comparing medians. Response rates were compared using contingency tables and Fisher exact test.

Investigational Review Board Approval
Investigators performed this trial after institutional review board (IRB) approval was obtained from and monitored by the Western IRB in Seattle, Washington. Each patient had given voluntary informed consent in writing before submission of tumor specimens for MiCK analysis. The clinical trial was registered at clinicaltrials.gov (NCT00901264).

RESULTS
The patient characteristics are described in Table 1. Mean age was >65 years, and 29 patients were female. A variety of tumors were studied, including breast (n = 16), non-small cell lung cancer (n = 6), non-Hodgkin lymphoma (n = 4), and others. Physicians most commonly entered patients who were being considered for palliative chemotherapy. Only 4 patients were entered who were being considered for adjuvant chemotherapy. The median line of therapy planned to be used for palliative care after the MiCK assay was second line, with a range of first-line treatment up to eighth-line treatment. The median time of follow-up for patients was 4.5 months (4.0 months in patients whose physicians did not use the MiCK assay vs 5.6 months in patients whose physicians used the MiCK assay to plan the treatments).

MiCK assay results were frequently used by physicians (Table 2); 64% of patients received chemotherapy based at least in part on the MiCK assay, and in 18 (41%) treatment was based only on the MiCK assay. In 10 patients (23%), physicians used MiCK results but also combined that information with other drugs not tested in the assay, or modified the assay results based on individual patient characteristics such as organ function and based on tumor biological characteristics. The biological characteristics of these varied tumors were considered by the oncologists in developing the final treatment plans. For example, in breast cancer, hormone-receptor positive patients received hormonal agents in addition to chemotherapy, and HER2-positive patients received trastuzumab in addition to chemotherapy. Patients with nonsmall cell lung cancer who were EGFR mutation-positive received erlotinib before consideration for performing the drug-induced apoptosis assay. CD20-positive non-Hodgkin lymphoma patients received rituximab in addition to chemotherapy. In 22 patients (50%), a change in chemotherapy resulted from using the MiCK assay results.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>44</td>
</tr>
<tr>
<td>Age, mean y</td>
<td>65.1</td>
</tr>
<tr>
<td>Female sex</td>
<td>29</td>
</tr>
<tr>
<td>Tumor types</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>16</td>
</tr>
<tr>
<td>Nonsmall cell lung</td>
<td>6</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
</tr>
<tr>
<td>Ovary</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Performance status (ECOG mean)</td>
<td>1.3</td>
</tr>
<tr>
<td>Line of therapy</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>4</td>
</tr>
<tr>
<td>1st</td>
<td>16</td>
</tr>
<tr>
<td>2nd</td>
<td>9</td>
</tr>
<tr>
<td>3rd</td>
<td>5</td>
</tr>
<tr>
<td>4th</td>
<td>1</td>
</tr>
<tr>
<td>5th or higher</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

### Table 2. Patterns of MiCK Assay Use

<table>
<thead>
<tr>
<th>Physician used MiCK assay</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used only the assay results</td>
<td>18</td>
</tr>
<tr>
<td>Used the assay and other data</td>
<td>8</td>
</tr>
<tr>
<td>Used assay plus other drugs</td>
<td>9</td>
</tr>
<tr>
<td>Used the assay but modified due to organ function</td>
<td>2</td>
</tr>
<tr>
<td>Physician did not use the MiCK assay results</td>
<td>16</td>
</tr>
<tr>
<td>Patient preferred not to use drugs</td>
<td>7</td>
</tr>
<tr>
<td>Patient put on clinical trial</td>
<td>1</td>
</tr>
<tr>
<td>Physician just did not use results</td>
<td>8</td>
</tr>
</tbody>
</table>
Although patients had signed consent to obtain the assay, in 16 instances the physician did not use the assay to determine patient treatment. In 1 instance, the patient entered a clinical trial. After being advised of the assay results and proposed treatment based on the assay, 7 patients preferred to be treated with another therapy (usually because of toxicity of the therapy identified as best in the MiCK assay). In the other 8 patients, the physician preferred to use another treatment based on literature or the physician’s personal experience.

In breast cancer, the largest subset of patients treated, 9 of 16 (56%) patients were treated based upon the MiCK assay. In 3 of 9, the MiCK assay was used with other nontested drugs, in 3 of 9 MiCK results were combined with targeted biotherapies, in 2 of 9 MiCK results were combined with hormonal therapy, and in 1 of 9 only the drugs active in the MiCK assay were used.

**Effect on Choices of Chemotherapy**

In 16 patients (36%), oncologists changed from an intended use of proprietary chemotherapy before knowledge of the MiCK assay to actual use of generic drugs after assay results were reviewed. In 3 (7%) of patients, physicians changed from intended use of generic drugs to actual use of proprietary drugs. In 9 patients (20%), physicians used single-drug therapy after the MiCK assay, compared with an intended use of combination therapy before knowing MiCK assay results. In 4 patients (9%), oncologists used combination therapy after MiCK assay results, compared with an intended use of single drugs before knowledge of the MiCK assay results.

When physicians used the MiCK assay, they used a chemotherapy that produced the highest KU value in 16 patients. Physicians used a treatment with a higher degree of apoptosis (>2 KU) in 23 patients.

**Effect on Patient Outcomes**

In patients receiving palliative chemotherapy, complete plus partial response rates were compared with the use or nonuse of the MiCK assay (Table 3). If physicians used the results of the MiCK assay, complete plus partial response rate was 44%. This compared with only 6.7% complete plus partial response rate if physicians did not use the MiCK assay ($P < .02$).

Overall survival was compared with use or nonuse of the MiCK assay results (Fig. 1). If physicians used the MiCK assay for determination of patient therapy, median overall survival was 10.1 months, compared with only 4.1 months if physicians did not use MiCK assay results ($P = .02$).

The relapse-free interval in patients whose physicians used the MiCK assay to determine therapy was compared with those patients whose physicians did not use the MiCK assay results (Fig. 2). The median relapse-free interval was 8.6 months in patients whose physicians used the MiCK assay, compared with 4.0 months in patients whose physicians did not use the MiCK assay ($P < .01$).

To rule out the possibility that the addition of other drugs to the chemotherapy selected based on the MiCK assay was responsible for the advantages observed when oncologists used the MiCK assay, we compared the results of patients whose oncologists used only the MiCK assay with the results of patients whose oncologists did not use the MiCK assay. Complete and partial response rates were higher in patients treated based only on the MiCK assay (43.8%), compared with patients treated without the use of the MiCK assay (6.7%, $P = .04$). Overall survival was longer in patients treated based only on the MiCK assay.

<table>
<thead>
<tr>
<th>MiCK Assay Use</th>
<th>CR</th>
<th>PR</th>
<th>Stable</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician used assay results</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Physician did not use assay results</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

*Table 3. Correlation of Response With MiCK Assay Use*

*Abbreviations: CR, complete response; PR, partial response.*
compared with patients treated without the use of the MiCK assay (median, 4.1 months; \(P = .02\)). The relapse-free interval was longer in patients treated based only on the MiCK assay (median, 8.0 months) compared with patients treated without the use of the MiCK assay (median, 4.0 months; \(P = .03\)). Thus, we conclude that the use of the MiCK assay (and not the addition of other drugs) was associated with the improved outcomes observed.

DISCUSSION
The issue of predictive testing for choosing chemotherapy for cancer patients is of very high interest. The MiCK assay is a nongenomic test that has demonstrated significant correlation with patient outcomes in ovarian cancer and in acute myelocytic leukemia, and is a predictive test that is currently undergoing additional prospective national trials in other tumors. This study was developed to determine whether and how physicians would use the assay when seeing results before proceeding with treatment.

This study was a nonrandomized trial, and therefore is an observational study. In this prospective multi-institutional clinical trial, the MiCK assay was frequently used by physicians to determine patient treatments. The 64% rate of use of this predictive bioassay by oncologists to design the chemotherapy treatment plan was considered to be evidence of clinical utility (physicians will use the results in patient care).

In many circumstances, physicians did not use the assay because of patient preferences (usually to avoid toxicity of drugs with best results in the assay). In only 1 instance was a patient placed on a clinical trial instead of using MiCK assay results. In patients in whom the physician elected not to use the assay results, oncologists just preferred to use a chemotherapy they were more comfortable with, or decided to use targeted therapy not tested in the assay based on other literature without patient bioassay results.

Because 8 of 28 patients whose physicians used the MiCK assay results were treated in addition with other drugs not tested in the assay (often biotherapy, targeted therapy, and/or hormonal therapy), the MiCK assay alone often will not determine a complete treatment plan. Other biomarkers were easily integrated with the MiCK assay results (especially estrogen receptors and HER2 analyses). The oncologists considered the biological characteristics of the tumors to guide treatment decisions in addition to the MiCK assay results in 23% of patients.

Because of the heterogeneity of the tumors studied, it is important that future studies be designed to compare, disease by disease, outcomes of patients in whom MiCK results were used, versus patients in whom MiCK results were used with other biomarker-selected drugs, versus patients in whom the MiCK assay was not used. In these studies, stratification and/or analysis of the patients by variables including histology, molecular analyses, and extent of disease will be necessary to make the conclusions more robust. Such studies are under way or being considered in UnitedHealthcare patients, and in centers such as Walter Reed National Military Medical Center and Vanderbilt Medical Center. Because this study was of a limited size (44 patients), the studies in progress or in development will add more patients with the same tumor type, at the same stage, and receiving the same line of therapy.

In 1 breast cancer patient whose results were important to note, the patient had received 8 prior lines of chemotherapy before a MiCK assay was performed. The physician had recommended hospice based on early progression on the last 2 lines of therapy and declining performance status. The patient and her husband initially had declined hospice because she had done well years earlier and they wanted to keep fighting. After the assay was performed, results demonstrated a low amount of apoptosis (0-1.5 KU) from 4 different drugs she had not previously received. The physician discussed these results with the patient and her family, which indicated only a low chance of response based on the MiCK assay results, and the likely associated toxicity with ineffective therapy. With this additional knowledge, the patient elected to
receive hospice care and stated that her decision was largely based on the low MiCK assay results. The MiCK assay may therefore be able to reduce inappropriate use of chemotherapy at the end of life and increase use of hospice services.

This study did not correlate the numerical KU value with results of therapy (response, duration of remission, or survival). Such a correlation is necessary in future studies, because it will be important to determine how high the KU must be to have an association with best outcomes for the individual patient. Larger studies of more homogeneous patient populations (eg, only breast cancer receiving first-line therapy for recurrent disease) will answer this question and define the optimal use of the assay. This study justifies the need for such studies, which are in progress.

Although this study had a relatively low accrual, the apparent overall survival and relapse-free interval were statistically significantly longer in those patients whose physicians’ management decisions were influenced by the MiCK assay. However, this initial study should be confirmed in larger subsequent trials. There could be many different reasons why an oncologist decided not to use the test (eg, patient declined the therapy, oncologists were not convinced of the improvement in outcomes if the results were used, the physician preferred another treatment based on clinical experience). Also, this was not a randomized study, and larger prospective randomized trials will help establish the magnitude of the improvement with use of the assay and correlation with actual KU values. The positive results in this trial are important because they serve as a rationale for conducting subsequent trials.

Despite the size of the study, the results indicate that not only are oncologists willing to use the results of the assay, but when they do, outcomes are likely to be superior to results when physicians do not use the assay. The magnitude of the improvement in these patients was large enough to be statistically significant.

This finding of improved outcomes may also reduce costs of care by avoiding use of less effective treatments. The observation that physicians often used less costly generic drugs may be important to oncologists by suggesting when generic drugs might be at least as useful as proprietary drugs. A modeling study of claims data from a large self-insured employer’s database has indicated that savings would have been likely if the MiCK assay had been used to select therapy. Although it is anticipated that use of inpatient hospital care, supportive care measures, and laboratory and radiologic evaluations could be reduced by use of the MiCK assay (because of longer and better disease control), this study did not address those variables. Such variables are being evaluated in future clinical utility trials (eg, a national utility trial underway in UnitedHealthcare patients). Future larger studies will examine, disease by disease, net cost savings for chemotherapy expenses and overall costs of care more comprehensively and interpret such results versus overall outcomes (relapse-free interval and overall survival). Such studies will also examine subsequent drug utilization to determine whether single-agent or generic drug use based on the MiCK assay actually replaces combination drug therapy and/or proprietary drug use, or simply delays it to a later line of therapy.

This is the first utility study to follow up on the prior trials of validity of the MiCK assay in ovarian cancer and acute myelocytic leukemia. Although all of the validation and utility trials have been prospective and multi-institutional, the validation trials were blinded so that the investigator never knew the MiCK assay results. This utility study was nonblinded, so that the oncologist received, within 72 hours of biopsy, the drug-induced apoptosis results and a laboratory interpretation of which therapies were best in vitro, and the actual KU of apoptosis for each single drug or combination tested. Although the outcomes were statistically significantly improved if the assay results were used by the oncologist, and although the results indicate that physicians will frequently use the assay results, larger correlative analyses will be able to determine which disease types and which lines of therapy are most impacted by use of the MiCK assay.

The strengths of this study are that the trial was prospective and multi-institutional, and it compared physician use with the important clinical outcomes of tumor response, relapse-free interval from time of assay, and overall survival. In addition, it was used on nonselected patients seen in community settings. The laboratory analyses were performed at some distance from the clinical sites (Montreal laboratory, clinical sites in Tennessee and Los Angeles), indicating applicability of the assay to all patients in the United States and Canada.

The weaknesses of the study are that it was small (44 patients), the sample of patients consisted of a heterogeneous group with different diagnoses and different lines of therapy, and the study was not randomized. Therefore, this study could not make individual conclusions about which diseases were most influenced by availability of the MiCK assay results. The study showed conclusively that overall the assay would be used in oncology patients, but hypothesis-generating for the questions as to whether the results are useful in adjuvant versus first-line versus later-line therapy, which type of cancer or leukemia is best impacted by the use of the assay, whether use of the assay...
alone or together with other nontested drugs is best, and whether there is an overall savings in health care costs by use of the assay. The results of this trial will help determine the anticipated benefits of assay use in future randomized trials, thus helping to determine the parameters and sample size required for high statistical power in such trials.

However, oncologists are frequently challenged by the need to make a choice about which therapy is best for an individual patient. Although molecular biomarker studies are widely viewed as an important aid in making such decisions, this study suggests that the MiCK assay may also be helpful to oncologists faced with making treatment decisions, and may be useful together with molecular results in the future. A trial is currently in development to integrate and correlate molecular and apoptosis assay results.

Because fresh tissue is needed for the MiCK assay, as well as for many other biomarker assays, not all patients at each line of therapy will have sufficient tissue available for analysis. Although currently the assay can be performed with excisional and incisional surgical biopsies (as well as with malignant effusions, bone marrow, and blood with adequate number of circulating leukemia or other neoplastic cells) and also with core needle biopsies, in the future, use of this assay might be more generally helpful if fine needle biopsies could be used. Studies are under way to develop such technology.

On the basis of this small multicenter trial, we conclude that when physicians are informed of the MiCK assay results, they frequently use the results to plan patient treatments. When physicians use the results, patient outcomes appear to be better. Continued collection of data on use of the MiCK assay and clinical outcomes will further define the clinical settings in which the assay is most helpful.

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CONFLICT OF INTEREST DISCLOSURES

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REFERENCES