Molecular Testing in the Management of Cardiac Transplant Recipients: Initial Clinical Experience

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Gene expression profiling (GEP) has recently been introduced as a new modality for cardiac allograft rejection monitoring. The test uses real-time polymerase chain reaction (PCR) technology to measure the expression of 20 genes (11 informative, 9 control and normalization). Using a multigene algorithm, a score ranging from 0 to 40 is generated. The score has been shown to discriminate between quiescence and moderate/severe acute cellular rejection in a large observational study and the GEP test has been used clinically since January 2005. The Working Group on Molecular Testing in Cardiac Transplantation was formed by cardiac transplant physicians, surgeons, pathologists and nurses with clinical interest and experience in the use of molecular testing. The goals of the group are to provide a summary of the initial clinical experience with molecular testing, provide recommendations for the clinical use of the GEP test based upon existing research and clinical data, and to define directions for clinical investigation.

Cardiac allograft rejection is experienced by 20% to 50% of patients at least once during the first year post-transplant under the present immunosuppression regimens.1–3 The standard for rejection surveillance has been the endomyocardial biopsy (EMB).4 However, EMB is invasive, causes morbidity, and is subject to sampling error and interobserver variability.5 As circulating peripheral blood mononuclear cells (PBMC) may reflect host responses to the allograft, measurement of PBMC gene expression should provide useful diagnostic information and reduce the need for EMB in certain clinical situations. Based on this hypothesis, a blood test was developed using DNA-microarray technology and real-time PCR. The test, which became available for clinical use in January 2005, measures the expression of 20 genes (11 informative, 9 control and normalization) by real-time PCR and provides a score ranging from 0 to 40, with lower scores being associated with a very low likelihood of moderate/severe cardiac allograft rejection, as defined by Grade ≥3A/2R, according to the original/revised International Society of Heart and Lung Transplantation (ISHLT) classification.4

EXISTING DATA ON GEP USE IN CARDIAC TRANSPLANT RECIPIENTS

The CARGO Study

The Cardiac Allograft Rejection Gene Expression Observational (CARGO) study was an observational study with the primary objective to develop and evaluate a GEP test from PBMC samples to discriminate between a quiescent state (ISHLT Grade 0 rejection; revised ISHLT Grade 0R) and moderate/severe rejection (original ISHLT Grade ≥3A/2R) in cardiac transplant recipients. Patients at eight heart transplant centers were followed prospectively with blood sampling performed at the time of post-transplant visits. Biopsies were graded by both local pathologists and by three independent core pathologists blinded to clinical data. Details on development and validation of the GEP test have been published elsewhere.6

The main finding from CARGO was that the GEP test could accurately detect the absence of moderate/severe...
rejection and thus identify a state of “quiescence” in the
allograft. The test distinguished moderate/severe biopsy-
defined rejection from quiescence ($p = 0.0018$) and
had an agreement of 84% (95% confidence interval [CI]:
66% to 94%) with ISHLT Grade $\geqslant$3A/2R rejection
compared with EMB. Beyond 1 year post-transplant,
patients with scores <30, representing approximately
68% of the study population, were very unlikely to have
Grade $\geqslant$3A/2R rejection (negative predictive value
[NPV] = 99.6%). Scores of <34 were also associated
with NPV for Grade $\geqslant$3A/2R rejection of >99%, which
is relevant based on the accrued clinical experience
with the GEP test discussed in what follows.

Variability of Biopsy “Gold Standard” and Relationship
to GEP Score

The CARGO study design originally assumed a gold
standard clinical end-point of biopsy-based detection of
acute cellular rejection. However, results from CARGO
demonstrated that this “gold standard” was limited by
considerable interobserver variability among local pathol-
gists, and use of GEP testing may help reduce the
variability of diagnosing acute cellular rejection inherent
in the biopsy. $^7$ Therefore, in the development and evalu-
ation of the GEP test, rejection was defined by a local
pathologist’s grading and by interpretation by a panel of
three experienced, independent, blinded pathologists
(central pathologists) who re-read each case. GEP
scores were progressively higher, on average, as the rate
of concordance among all pathologists’ readings increased
for identifying Grade $\geqslant$3A/2R rejection. When one of four
pathologists diagnosed Grade $\geqslant$3A/2R, the average GEP
score was 28.5. When four of four agreed on Grade
$\geqslant$3A/2R, the average GEP score was 33. $^8$

Discordance of GEP Score With Biopsy: Potential
Explanations

Clearly, the situation can arise where the GEP score is
discordant from the histologic grading. A “positive
biopsy” ($\geqslant$3A/2R) and low GEP score (<34) is uncom-
mon but may hypothetically be seen when local patholo-
gists misdiagnose rejection, either overgrading or mis-
interpreting (e.g., Quilty lesions) the histology. $^7$ In
addition, a sub-set of focal rejection may be benign: in
one study, >90% of Grade 3A biopsies with two foci of
focal moderate rejection, diagnosed after 1 year post-
transplant, resolved without therapy. $^9$ Finally, molecu-
lar testing and biopsy measure different processes,
which may be discordant (e.g., lagging clearance of
infiltrate in “resolving rejection”). In the CARGO study,
rates of positive biopsy and low molecular score were
low. For example, with a threshold score of 34 beyond
1 year post-transplant, the NPV of the test for Grade
$\geqslant$2R/3A rejection was 99.2% (Table 1). Thus, a Grade
$\geqslant$2R/3A would be expected to occur with a low GEP
score in 8 of 1,000 tests in a population similar to
CARGO.

Conversely, a “negative biopsy” and high molecular
score may be observed. Several hypotheses may explain
this phenomenon, including early or focal rejection that
may not be detected on the biopsy due to sampling error,
alloimmune activation in the absence of cellular rejection
on the biopsy, immune activation relating to conditions
other than acute cellular rejection (e.g., antibody-medi-
ated rejection, cardiac allograft vasculopathy/chronic re-
jection or infection), and a quiescent state in a chronic
and clinically stable heart transplant recipient. In the
CARGO study, the rate of samples tested that had a
negative biopsy with a high AlloMap score increased
with time post-transplantation.

Effect of Time Post-transplantation on Performance
of GEP Test

Samples from CARGO were used to derive the perfor-
nance characteristics for the GEP test across a range of
scoring thresholds (Table 1). Because rejection rates
and average GEP scores are known to vary with time
post-transplant, $^6$ performance characteristics are re-
ported for defined time intervals (<6 months, 6 to 12
months and ≥12 months). NPV and positive predictive
value (PPV) are reported for each threshold with re-
spect to Grade $\geqslant$3A/2R rejection as defined by local and
central pathologists. The percent of patients above
threshold is the estimated overall rate of positive tests
for an outpatient population. When interpreting the
PPV for the GEP test for Grade $\geqslant$3A/2R rejection, it
must be recognized that this parameter is highly depen-
dent on the time-dependent prevalence of rejection in
this population. In the first 6 months post-transplant,
the risk of rejection is significantly higher than in later
periods, and the PPV of the GEP test can be as high as
20% to 40% with high scores (Table 1). Beyond 1 year
post-transplant, the rate of Grade $\geqslant$3A/2R rejection
drops to low levels (<3% of biopsies in CARGO), and
the PPV of the test declines as well. This phenomenon
is important to consider when interpreting high scores
in patients at ≥1 year post-transplant, who are at low
risk for rejection. The expectation in the majority of
these patients is that they do not have concurrent Grade
$\geqslant$3A/2R rejection on biopsy.

The GEP score associated with quiescence also rises
with time post-transplant, probably related to down-
titration of corticosteroids and overall immunosuppres-
sion. Because the risk of rejection decreases with time
and the NPV of the GEP score remains high over the
range of a score of 30 to 35, the data allow for use of
higher GEP score thresholds for patients during later
periods post-transplant to identify patients at very low
risk for rejection. Thus, the initial clinical experience
implementation guidelines of GEP thresholds vary by
time post-transplant (>2 to 6 months, 6 to 12 months, ≥12 months post-transplant). It is also important to consider that the incidence of rejection diminishes as time post-transplant elapses, implying excellent sensitivity but low specificity.

**Relationship of GEP Scores to Corticosteroid Dose**

Quiescent GEP scores rise with time post-transplant throughout the first year, with the steepest part of this rise in the first 6 months. Corticosteroid dosing is the clinical variable most strongly associated with this pattern. Expression of a number of genes in the GEP algorithm correlates with steroid dose (ITGAM, IL1R2 and FLT3). The pattern of change in expression of these genes with decreasing steroid dose is the same as the pattern observed with rejection. Steroid dosing is rapidly reduced in the first 6 months and progressively lowered during the remainder of the first year and beyond. Available data from the CARGO registry suggest that prednisone doses of ≤20 mg/day do not significantly influence the GEP score.

**Relationship of GEP Scores to Cytomegalovirus Infection**

Of 171 samples from 104 CARGO patients tested, 13 (8%) had cytomegalovirus (CMV) detected by quantitative PCR. Eighteen genes correlated with CMV viremia (p < 0.05). These genes were involved in T-cell activation (Granzyme B, LAG3) and anti-viral response and host defense (Viperin, interferon-γ). A sub-set of these genes were previously known to correlate with CMV infection. No correlation was detected between plasma CMV PCR positivity and acute rejection (ISHLT Grade ≥2) at the time of sample acquisition or at subsequent follow-up times. Initial analysis showed that the pattern of gene expression from subjects with PCR-detectable CMV did not significantly overlap with that of acute rejection, and CMV status had no significant impact on the acute rejection gene expression pattern or GEP score. The impact of other infections has not been studied; however, the GEP genes did not show overlap with genes and pathways identified in a recent review of the host molecular response to infection.

**CLINICAL EXPERIENCE WITH GEP TESTING**

**Early Post-CARGO Clinical Data**

The GEP test, also known as the AlloMap, has been commercially available through the Clinical Laboratory Improvement Amendment (CLIA)-certified XDx, Inc.,

| Table 1. GEP Performance Metrics Estimated From the CARGO Patient Populationa |
|---|---|---|---|---|
| AlloMap score | >2 to <6 months post-transplant (n = 440) | 6–12 months post-transplant (n = 239) | >12 months post-transplant (n = 111) |
| % Above | PPV ≥ 3A | NPV < 3A | % Above | PPV ≥ 3A | NPV < 3A | % Above | PPV ≥ 3A | NPV < 3A |
| 16 | 85.2% | 4.0% | 100.0% | — | — | — | — | — | — |
| 17 | 82.6% | 4.2% | 100.0% | — | — | — | — | — | — |
| 18 | 80.5% | 4.1% | 99.2% | — | — | — | — | — | — |
| 19 | 77.0% | 4.3% | 99.3% | 90.8% | 2.8% | 100.0% | — | — | — |
| 20 | 75.0% | 4.4% | 99.4% | 88.0% | 2.9% | 100.0% | — | — | — |
| 21 | 67.6% | 4.4% | 98.6% | 85.6% | 3.0% | 100.0% | — | — | — |
| 22 | 63.8% | 4.7% | 98.7% | 83.7% | 3.0% | 100.0% | — | — | — |
| 23 | 58.8% | 4.5% | 98.1% | 79.9% | 3.2% | 100.0% | — | — | — |
| 24 | 53.4% | 4.7% | 98.0% | 76.5% | 3.3% | 100.0% | — | — | — |
| 25 | 48.0% | 4.9% | 97.9% | 76.5% | 4.1% | 100.0% | 80.7% | 2.8% | 100.0% |
| 26 | 43.7% | 5.0% | 97.8% | 71.6% | 4.4% | 100.0% | 74.7% | 3.0% | 100.0% |
| 27 | 39.6% | 5.1% | 97.7% | 65.9% | 3.9% | 98.2% | 70.4% | 2.9% | 99.3% |
| 28 | 35.2% | 5.3% | 97.6% | 58.4% | 3.9% | 98.6% | 63.4% | 3.2% | 99.4% |
| 29 | 30.1% | 5.2% | 97.3% | 54.3% | 3.6% | 98.7% | 57.5% | 3.5% | 99.5% |
| 30 | 25.4% | 6.2% | 97.5% | 43.7% | 3.2% | 98.4% | 50.8% | 4.0% | 99.6% |
| 31 | 20.7% | 6.1% | 97.2% | 38.9% | 3.6% | 98.5% | 43.2% | 4.7% | 99.6% |
| 32 | 15.9% | 5.9% | 97.0% | 32.1% | 3.5% | 98.2% | 31.9% | 5.5% | 99.4% |
| 33 | 12.3% | 6.4% | 97.0% | 25.1% | 4.5% | 98.4% | 26.6% | 5.7% | 99.4% |
| 34 | 8.9% | 8.8% | 97.1% | 18.0% | 4.7% | 98.5% | 22.3% | 5.6% | 99.2% |
| 35 | 5.8% | 10.7% | 97.0% | 12.6% | 4.5% | 98.3% | 16.3% | 6.2% | 99.0% |
| 36 | 3.1% | 15.1% | 96.9% | 7.5% | 7.5% | 98.4% | 12.4% | 6.1% | 98.8% |
| 37 | 1.7% | 27.8% | 97.0% | 3.1% | — | 97.8% | 7.7% | 9.9% | 98.8% |
| 38 | 0.5% | 28.5% | 96.7% | 1.3% | — | 97.9% | 4.0% | — | 98.4% |
| 39 | 0.0% | — | 96.6% | 0.9% | — | 97.9% | 3.1% | — | 98.5% |

*aPerformance is given by time post-transplant.*
reference laboratory, and has been used clinically by U.S. transplant centers since January 2005. Experience with rejection surveillance protocols incorporating GEP testing has provided additional insight into the performance characteristics of this test when used in a real-time clinical setting. To date, transplant centers have used the AlloMap test in conjunction with the biopsy or in lieu of the biopsy in patients who are ≥6 months post-transplant and at low risk for rejection. In addition, AlloMap testing has been used to non-invasively exclude rejection in patients with ambiguous signs or symptoms, in patients with inadequate biopsy specimens, and in patients with difficult vascular access.

Because of the effect of time post-transplant on GEP scores and the lower risk of rejection in patients beyond the first year, some centers have chosen, from the spectrum of options summarized in Table 1, a threshold of <34 to identify patients who may be managed without a biopsy. A second important observation derived from clinical experience is that a sub-set of patients have consistently high longitudinal AlloMap scores yet do not have associated Grade ≥3A/2R rejection on their biopsies. Therefore, some centers have discontinued biopsies or reverted to non-invasive rejection surveillance protocols in patients with consecutively high AlloMap scores and quiescent biopsies. The clinical significance of an AlloMap score above threshold with a concurrent quiescent heart biopsy is unknown, is likely dependent on time post-transplantation, and requires further investigation.

The pooled clinical data from several transplant centers (follow-up date: March 31, 2006) are summarized in Tables 2, 3, 4 and 5 and Figures 1 and 2. There were 243 clinical AlloMap measurements included, 32 (13.2%) during the 6- to 12-month period, 192 (79.0%) during the 1- to 5-year period, and 19 (7.8%) during the >5-year period. The most important observation was the CARGO study confirmation of a high negative predictive value (100%) with respect to biopsies of Grade ≥2R/3A. It should be recognized that the mean duration post-transplant in this cohort was longer than the 14.5 months in the CARGO study. The data suggest that the test characteristics, when applied to patients who are ≥6 months post-transplant, are similar to those derived from the CARGO study. However, in this patient population, a higher test threshold (<34), which still maintains an excellent negative predictive value of >99%, may be appropriate as the GEP scores tend to rise with time post-transplant in clinically stable patients with histologically confirmed “quiescence” (Figure 1A).

### Candidates for GEP Testing

GEP testing is being used in clinically stable cardiac transplant recipients who are ≥15 years of age and ≥6 months post-transplant to identify patients at low risk for moderate/severe (Grade ≥3A/2R) cellular rejection. The frequency of rejection surveillance using the GEP test should be individualized to the patient’s rejection history, immunosuppression regimen, time post-transplant and transplant center protocol. At the time of GEP testing, a thorough history and physical examination is obtained/performed by an appropriately trained transplant physician, and a non-invasive assessment of cardiac allograft function utilizing echocardiography is performed to evaluate allograft function (Figure 2).

In contrast, GEP testing is not used:

- In patients at high risk for acute rejection or graft failure, including those with: (a) signs/symptoms of cardiac allograft dysfunction or hemodynamic

### Table 2. Pooled AlloMap Test Scores and Endomyocardial Biopsy Data: Distribution by Time Elapsed After Transplantation

<table>
<thead>
<tr>
<th>Time Elapsed</th>
<th>n (%)</th>
<th>6–12 months, n (%)</th>
<th>1–5 years, n (%)</th>
<th>&gt;5 years, n (%)</th>
<th>Total, n (%)</th>
<th>&gt;1 year, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AlloMap test encounters</td>
<td>32 (13.2)</td>
<td>192 (79.0)</td>
<td>19 (7.8)</td>
<td>243</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td>AlloMap score &lt;34</td>
<td>26 (10.7)</td>
<td>133 (54.7)</td>
<td>14 (5.8)</td>
<td>173</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>AlloMap score ≥34</td>
<td>6 (2.5)</td>
<td>59 (24.3)</td>
<td>5 (2.1)</td>
<td>70</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Total patients: 118.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Pooled AlloMap Test Scores and Endomyocardial Biopsy Data: Distribution and ISHLT Grades at 1 Year After Transplantation

<table>
<thead>
<tr>
<th>ISHLT grade</th>
<th>n (%)</th>
<th>&lt;2R</th>
<th>≥2R</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2R</td>
<td>206 (97.6)</td>
<td>2 (0.9)</td>
<td>208 (99.0)</td>
<td></td>
</tr>
<tr>
<td>AlloMap score &lt;34</td>
<td>147 (69.7)</td>
<td>147 (69.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥34</td>
<td>64 (30.3)</td>
<td>64 (30.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>211</td>
<td>211</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Where Grade ≥2R = ≥3A.

### Table 4. Pooled AlloMap Test Scores and Endomyocardial Biopsy Data: Incidence of Disagreement (Discordance) of ISHLT Grades and AlloMap Test Scores 1 Year After Transplantation

<table>
<thead>
<tr>
<th>ISHLT grade</th>
<th>AlloMap score</th>
<th>n (%)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2R</td>
<td>&lt;34</td>
<td>147</td>
<td>69.7</td>
</tr>
<tr>
<td>&lt;2R</td>
<td>≥34</td>
<td>59</td>
<td>28.0</td>
</tr>
<tr>
<td>≥2R</td>
<td>&lt;34</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>≥2R</td>
<td>≥34</td>
<td>5</td>
<td>2.4</td>
</tr>
</tbody>
</table>
compromise (including LV ejection fraction <40% and cardiac index <2 liters/min); (b) recurrent Grade ≥3A/2R cellular rejection (≥2 episodes within the past year); or (c) a history of Grade ≥3A/2R cellular rejection within the preceding 6 months or antibody-mediated rejection within the preceding 12 months.

- In pregnant women.
- In patients who have had a blood transfusion in the previous 30 days.
- In patients who have received hematopoietic growth factors affecting leukocytes within the previous 30 days.
- In patients who have received high-dose steroids (intravenous bolus or oral augmentation) within the past 21 days or who are currently on ≥20 mg/day of prednisone equivalent.
- In patients <15 years of age.

### Interpretation of GEP Score: Threshold

In patients who are >2 months post-transplant, have an AlloMap score of <20, and are >6 months post-transplant, an AlloMap score of <30 is associated with a very low risk of cellular rejection. It is reasonable not to perform a biopsy when the AlloMap score falls below this threshold. In patients ≥1 year post-transplant, a higher threshold of <34 is often used. Patients with AlloMap scores above threshold should undergo EMB as soon as feasible, although most episodes of moderate rejection are asymptomatic and not associated with allograft dysfunction.

In some centers participating in the clinical implementation, patients beyond 1 year post-transplant who have two or more consecutive AlloMap scores above threshold are considered for management without a surveillance biopsy if:

- There was no evidence of treatable rejection on the two previous biopsies.
- There is no statistically significant increase in AlloMap score (A score is considered statistically different from a previous one if the previous score does not fall within the 95% confidence interval of the current score).
- There have been no major interim changes in immunosuppression.
- There is no clinical or laboratory manifestation of graft dysfunction.

Clinicians in other centers participating in the initial implementation continue their conventional invasive rejection surveillance protocol in this situation, because the significance of chronically elevated AlloMap scores in this setting is currently unknown.

There are numerous factors that may increase the risk of rejection and poor outcomes in heart transplant recipients, including demographic factors, baseline AlloMap score, history of rejection or immunosuppressive regimen. These factors should be considered in the
selection of a threshold for an individual patient in order to optimize decisions about use of biopsy or rejection therapy.

**FUTURE DIRECTIONS AND CLINICAL RESEARCH PERSPECTIVES**

Although the GEP test was originally developed and validated to discriminate between patients with absence of rejection (quiescence) and those with moderate/severe cellular rejection, much interest has focused on the ability of the test to predict future rejection. Other areas of interest include risk stratification of patients with uncertain clinical or pathologic profiles, detection of antibody-mediated rejection and cardiac allograft vasculopathy (CAV), and guidance of early corticosteroid weaning and long-term immunosuppression down-titration to minimize the risks of immunosuppression-related chronic toxicities and complications. Furthermore, the CARGO study showed that a sub-set of patients with mild (current ISHLT Grade 1R) cellular rejection had elevated GEP scores, suggesting that patients with Grade 1R rejection may represent a heterogeneous group with variable levels of alloimmune activation and risk of future rejection or clinically important events affecting the allograft.

Studies evaluating the role of the GEP test in each of these scenarios are currently in progress and their findings should provide additional insight into use of the test in these conditions. For example, the CARGO II study is currently underway at 13 transplant centers in North America and Europe. The goals of this large observational study, with a targeted enrollment of 500 patients, are to evaluate the ability of the GEP test to predict both current and future acute cellular rejection, to detect antibody-mediated rejection and transplant vasculopathy, to validate the GEP test in an international patient population, and to investigate its potential for tailoring and individual-
izing immunosuppressive medications. Future studies will also be needed to evaluate the clinical significance of persistently high GEP scores in the absence of biopsy-detected rejection, to determine the impact of mTOR inhibitors and newer immunosuppressive agents on GEP scores, and to validate the performance of the test in patients <15 years of age.

Finally, although the performance of the GEP test has been validated in a large number of transplant patients, the clinical outcomes associated with using a GEP-based strategy, as compared with a biopsy-based strategy, for assessing rejection in heart transplant recipients who are 2 to 5 years post-transplant. The study, “Invasive Monitoring Attenuation through Gene Expression (IMAGE),” will evaluate the impact of these two strategies with respect to clinical outcomes, using meaningful indicators of acute cardiac allograft rejection such as graft dysfunction, clinically apparent rejection and death, as well as incidence of biopsy-related complications, quality of life and resource utilization as end-points.

APPENDIX
The following individuals participated in the Working Group on Molecular Testing in Cardiac Transplantation, in addition to the authors: Linda Addonizio, MD; E. Joseph Bauerlein, MD, FACC; Daniel Bernstein, MD; Martin Cadeiras, MD; Maryanne R. K. Chrisant, MD; Marisa Crespo, MD; R. Douglas Ensley, MD; David Feldman, MD, PhD, FACC; Michael Felker, MD, MHS, FACC; Shelley Hankins, MD; Jud Hunt, MD; Frances L. Johnson, MD; Maryl R. Johnson, MD; Shaf Keshavjee, MD; A. G. Kfoury, MD, FACC; Joan Miller, RN; Seema Mital, MD; Paraic Mulgrew, MD; Srinivas Murali, MD; Myhung H. Park, MD, FACC; Jignesh Patel, MD, PhD; Daniel Pauly, MD, PhD; David Pelegrin, RN, PA; Si Mai Pham, MD, FACS, FAHA; Barbara Pisani, DO, FACC; Branislav Radovancevic, MD; Dale Renlund, MD; Theresa M. Rowe, RN, MSN, CRNP, CCTC; Marc J. Semigran, MD; Frank Smart, MD; Josef Stehlik, MD, MPH; Jeffery J. Teuteberg, MD; Adrian Van Bakel, MD; Jeffrey H. Walden, MD; and Celeste Williams, MD.

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