Optimizing Personalized Bone Marrow Testing Using an Evidence-Based, Interdisciplinary Team Approach

Adam C. Seegmiller, MD, PhD,1 Annette S. Kim, MD, PhD,1 Claudio A. Mosse, MD, PhD,1,2 Mia A. Levy, MD, PhD,3,4 Mary Ann Thompson, MD, PhD,1 Megan K. Kressin, MD,1,2 Madan H. Jagasia, MBBS,4 Stephen A. Strickland, MD,4 Nishitha M. Reddy, MD,4 Edward R. Marx, MBA,5 Kristy J. Sinkfield, MEd,6 Herschel N. Pollard, MS,6 W. Dale Plummer,7 William D. Dupont, PhD,7 Edward K. Shultz, MD,1,3 Robert S. Dittus, MD, MPH,4,8,9 William W. Stead, MD,3,6 Samuel A. Santoro, MD, PhD,1 and Mary M. Zutter, MD1

From the 1Departments of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, TN; 2Department of Pathology and Laboratory Medicine, VA Tennessee Valley Healthcare System, Nashville, TN; 3Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN; 4Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN; 5Office of the Vice Chancellor for Health Affairs, Vanderbilt University School of Medicine, Nashville, TN; 6Office of Strategy and Transformation, Vanderbilt University School of Medicine, Nashville, TN; 7Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN; 8Institute for Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, TN; and 9Geriatric Research, Education and Clinical Center, VA Tennessee Valley Healthcare System, Nashville, TN.

Key Words: Hematopathology; Informatics; Molecular diagnostics; Genetics

ABSTRACT

Objectives: To address the overuse of testing that complicates patient care, diminishes quality, and increases costs by implementing the diagnostic management team, a multidisciplinary system for the development and deployment of diagnostic testing guidelines for hematologic malignancies.

Methods: The team created evidence-based standard ordering protocols (SOPs) for cytogenetic and molecular testing that were applied by pathologists to bone marrow biopsy specimens on adult patients. Testing on 780 biopsy specimens performed during the six months before SOP implementation was compared with 1,806 biopsy specimens performed during the subsequent 12 months.

Results: After implementation, there were significant decreases in tests discordant with SOPs, omitted tests, and the estimated cost of testing to payers. The fraction of positive tests increased. Clinicians reported acceptance of the new procedures and perceived time savings.

Conclusions: This process is a model for optimizing complex and personalized diagnostic testing.

Personalized medicine promises customized diagnosis and individualized therapies based on an individual’s genotype. This requires application of an increasing number of complex and expensive diagnostic analyses. Unfortunately, there are few standards or decision support mechanisms to assist physicians in test selection and interpretation. This often results in excessive and unnecessary testing1-4 that compounds the complexity of patient care, lowers quality of care, and increases health care costs in a system increasingly conscious of efficiency and value.5-7

Evidence-based clinical decision support systems have improved practitioner performance and decision making.8-17 Thus, to address the challenge of testing complexity, a team of practicing physicians, pathologists, and biomedical informaticians (the diagnostic management team or DMT) developed an approach to optimize complex diagnostic testing. The goals included development of evidence-based standards for ancillary testing, integration and interpretation of test results, implementation of the strategy into clinical work process through electronic medical records, and evaluation of the impact of changes.

Neoplastic hematology is at the forefront of personalized medicine. The classification and treatment of hematolymphoid malignancies are based on underlying genetic abnormalities18 and emerging targeted therapies for leukemia and lymphoma requiring tumor genetic testing.19,20 Thus, the initial DMT effort focused on diagnosis, classification, monitoring, and interpretation of results for patients with hematologic malignancies. We demonstrate that the approach was effective in reducing the total number of ordered cytogenetic
and molecular tests, decreasing the omission of recommended tests, and cutting the cost of laboratory testing to payers while achieving acceptance among ordering providers. Although this work highlights the impact on hematologic malignancies, potential application of this approach is broad and could include a wide range of clinical scenarios.

Materials and Methods

The DMT

The DMT is a collaboration among experts from three groups: pathologists representing hematopathology, immunopathology, cytogenetics, and molecular diagnostic laboratories; hematologists and hematology nurse practitioners; and biomedical informaticians. These individuals jointly analyzed current practices and developed new processes and guidelines for complex testing.

Development and Implementation of Standard Ordering Protocols

DMT members designed standard ordering protocols (SOPs) that define sets of recommended cytogenetic and molecular tests to be ordered on bone marrow specimens for patients with certain hematologic malignancies in particular clinical scenarios. SOPs were primarily based on published evidence and clinical guidelines. If there were no relevant evidence or guidelines, SOPs followed mutually agreed on best clinical practices based on these principles: tests were ordered at initial diagnosis if useful for diagnosis or subclassification, monitoring response to therapy, or prognostication; tests were ordered for follow-up biopsy specimens if positive at diagnosis and sensitive for residual disease detection; and where multiple modalities existed for the same abnormality, the most sensitive test was used. An example SOP (for acute myeloid leukemia and myelodysplastic syndrome [AML/MDS]) is shown in Table I.

SOPs were developed for acute lymphoblastic lymphoma, AML/MDS, bone marrow failure (BMF) and cytopenias of unknown etiology, lymphoma, myeloproliferative neoplasms, and plasma cell myeloma in adult patients. Test recommendations were made for five clinical scenarios: initial diagnosis or other morphologically overt disease, lymphoma staging, monitoring during and after therapy without overt disease, evaluation prior to stem cell transplant (pre-SCT), and monitoring following transplant (post-SCT). The SOPs were reviewed, modified, and approved by the entire team of hematopathologists and hematologists at Vanderbilt.

New ordering procedures were instituted with two options: (1) DMT testing, in which tests were ordered by pathologists based on SOPs, patient history provided by clinicians, and preliminary examination of the specimen by microscopy and flow cytometry, and (2) non-DMT testing, in which hematologists ordered tests individually based on their clinical judgment. The DMT testing procedures were approved by the Vanderbilt University Medical Center Medical Board.

Test Utilization Analysis

This study was approved by the Institutional Review Board of Vanderbilt University. Test selection and results were evaluated for all adult bone marrows obtained 26 weeks prior and 52 weeks subsequent to DMT implementation (February 14, 2011). Medical records were examined to determine the following: diagnostic and clinical category, number and type of tests performed, and whether test results were positive (abnormal) or negative (normal). The examiners (A.C.S., A.S.K., C.A.M., and M.K.K.) also compared the tests ordered with the appropriate SOP and determined whether the tests were concordant (recommended) or discordant (not recommended) with SOPs and whether any recommended tests were omitted. The examiners were masked as to whether

### Table I

<table>
<thead>
<tr>
<th>Tests</th>
<th>Diagnosis or Overt Disease</th>
<th>Monitoring: No Overt Disease</th>
<th>Pre-SCT</th>
<th>Post-SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometry</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Yes</td>
<td>Yes</td>
<td>Any previous positive</td>
<td>Any previous positive</td>
</tr>
<tr>
<td>FISH</td>
<td>AML and/or MDS panelb</td>
<td>NPM1b</td>
<td>NPM1 or FLT3 (if previously positive)</td>
<td>NPM1 or FLT3 (if previously positive)</td>
</tr>
<tr>
<td>Molecular</td>
<td>FLT3 ITD</td>
<td>c-Kitc</td>
<td></td>
<td>Bone marrow engraftmentd</td>
</tr>
<tr>
<td></td>
<td>NPM1b</td>
<td>CEBPAc</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; SCT, stem cell transplant.

b AML panel consists of FISH tests for t(8;21), t(15;17), inv(16), and 11q23. MDS panel consists of FISH tests for chromosomes 5p/5q, 7q, 8, and 20q. Panels are chosen based on clinical setting and morphologic appearance at diagnosis. Only individual previously positive FISH tests are ordered on subsequent specimens with overt disease.

c NPM1 is only ordered in cases with normal karyotype.
d Bone marrow engraftment refers to the molecular profiler assay for restriction fragment length polymorphisms, if informative, or XY FISH if the profiler assay is not informative, performed for allogeneic transplants only.
DMT or non-DMT testing procedures were followed. The data were collected into a REDCap database (http://redcap.vanderbilt.edu).21

The outcome measures for this analysis were percent utilization of DMT protocols; total number of ancillary tests ordered per marrow, categorized as concordant and discordant with SOPs; and fraction of tests with positive results. DMT use was defined as the weekly fraction of specimens for which DMT testing was selected by the ordering clinician. In the analysis of discordant positive tests, redundant tests were defined as multiple tests of different modalities that detect the same abnormality. A potential false-positive test was defined as a test that was positive, usually at low levels, in the current bone marrow but negative in prior and/or subsequent bone marrows.

Financial Analysis

Cost analysis was performed from a blended payer perspective (Medicare, Medicaid, and commercial insurance). The average reimbursement paid to Vanderbilt University Medical Center for each test was determined for Medicare. A multiplier was then used to arrive at the blended rate for all payers. The multiplier was based on the payer mix and contracted rates for pathology services at Vanderbilt. The cost per test was held constant across the entire period to control for any price fluctuations due to reimbursement changes. The cost of testing per sample was a summation of the average charges for each test ordered on that bone marrow.

National annual bone marrow volume was estimated using data from the National Cancer Institute Surveillance, Epidemiology and End Results database,22 which indicated 145,173 new diagnoses of lymphoma, leukemia, and myeloma in the United States for 2009. This figure was multiplied by the ratio of annual bone marrow biopsies to new diagnoses at Vanderbilt (4.59) to estimate a national annual bone marrow volume of 666,000.

Clinician Survey

Thirty-four clinicians, including hematologists and nurse practitioners, were surveyed anonymously using a RedCap survey tool21 to determine perceptions of DMT acceptance, value, and impact. Of these, 22 (65%) responded. Applicable survey statements and answers are listed in Table 2.

Statistical Analysis

Our primary analysis plan was to model the number of discordant, concordant, and omitted bone marrow tests as a function of time, starting six months prior to the implementation of the DMT’s SOPs and extending for the following year. We did this using a restricted cubic spline 5-knot linear autoregressive moving average (ARIMA) model.23,24 The location of the model knots were chosen as recommended by Harrell.25 We used Akaike’s information criterion (AIC) to compare each linear regression model with analogous first-order moving average, first-order autoregressive, and combined first-order autoregressive-moving average ARIMA models.26 Our models all gave similar results, with the linear regression models having the lowest AIC. For this reason, the analyses presented here are based on multiple linear regression models with independent error terms. The fact that these models performed best is not surprising given that individual patients did not give multiple bone marrow samples over short periods, making the results on consecutive days independent of each other. We also evaluated models with individual covariates for each day of the week. The parameters for these covariates were not significantly different from zero, and adding these covariates did not improve the AIC values. For these reasons, these day-of-the-week covariates were dropped from further consideration. We also ran models with 4 and 6 knots. As judged by AIC values, the 4-knot model did not fit the data as well as the 5-knot model, and there was a trivial improvement associated with the 6-knot model. For this reason, we elected to use our 5-knot model.

<table>
<thead>
<tr>
<th>Survey Statements</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly Disagree</td>
<td>Strongly Agree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I trust the pathologists to order appropriate tests for my patients.</td>
<td>1/22 (5)</td>
<td>0/22 (0)</td>
<td>3/22 (14)</td>
<td>8/22 (36)</td>
<td>10/22 (45)</td>
</tr>
<tr>
<td>2. I trust the SOPs to help the pathologists choose the right tests at the right time for my patients.</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>3/21 (14)</td>
<td>10/21 (48)</td>
<td>8/21 (38)</td>
</tr>
<tr>
<td>3. I prefer to be the individual primarily responsible for deciding which tests should be ordered on my patients.</td>
<td>8/22 (36)</td>
<td>6/22 (27)</td>
<td>7/22 (32)</td>
<td>1/22 (5)</td>
<td>0/22 (0)</td>
</tr>
<tr>
<td>4. Ordering the bone marrow testing panel saves me time.</td>
<td>0/22 (0)</td>
<td>1/22 (5)</td>
<td>2/22 (9)</td>
<td>7/22 (32)</td>
<td>12/22 (54)</td>
</tr>
<tr>
<td>5. Implementation of the hematopathology DMT improves cost containment.</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>4/20 (20)</td>
<td>6/20 (30)</td>
<td></td>
</tr>
<tr>
<td>6. I prefer the “old way” (a la carte) of test ordering and test result display (ie, I would “turn off” the DMT).</td>
<td>10/21 (48)</td>
<td>9/21 (43)</td>
<td>2/21 (9)</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
</tr>
</tbody>
</table>

DMT, diagnostic management team; SOP, standard ordering protocol.
After we had started our analyses, we noticed that the number of patients per day undergoing bone marrow biopsies increased during the course of this study. To account for this increase, we included the daily bone marrow count in our model. In summary, our final models used multiple linear regression to regress the number of tests (discordant, omitted, etc) against 5-knot restricted spline covariates derived from the date of the bone marrow biopsy; these models were also adjusted for the number of patients biopsied each day.

We also used Poisson regression to compare the cost per patient in the six months prior to the DMT intervention with that obtained one year later. A bias-corrected 95% confidence interval (CI) for the difference in the cost per patient in these intervals was estimated by bootstrapping. Categorical data were compared using the Fisher exact test by GraphPad Prism (version 5; GraphPad Software, La Jolla, CA).

**Results**

**Test Utilization**

The hematopathology DMT is a multidisciplinary team of hematologists, hematopathologists, and biomedical informaticians that designed evidence-based SOPs to define appropriate cytogenetic and molecular test ordering for bone marrow biopsies (see Materials and Methods). Beginning with DMT implementation (February 14, 2011), clinicians performing bone marrow biopsies either ordered tests based on their clinical judgment (traditional, non-DMT testing) or ordered the DMT process requesting that the pathologist select tests based on the SOPs after initial examination of the specimen (DMT testing).

To establish a baseline, we analyzed bone marrow test utilization for six months prior to DMT intervention with that obtained one year later. A bias-corrected 95% confidence interval (CI) for the difference in the cost per patient in these intervals was estimated by bootstrapping. Categorical data were compared using the Fisher exact test by GraphPad Prism (version 5; GraphPad Software, La Jolla, CA).

**Financial Impact**

To assess the effect of SOP implementation on testing costs, we estimated the expense to health care payers of the tests performed (see Materials and Methods). Testing cost varied significantly with time, similar to total tests (Figure 2D). The average cost per bone marrow in the six months preceding SOP implementation was $2,390, while the corresponding cost one year later was $1,948, a difference of $442 (95% CI, $290-$594; P < .001).

Based on our yearly institutional volume of approximately 1,800 adult bone marrow specimens, this represents a yearly savings to payers of $522,000 to $1,069,200. Extrapolation of these numbers to the estimated national annual bone marrow volume of 666,000 (see Materials and Methods)
indicates an estimated national savings opportunity to payers of $191 to $392 million per year.

**Validity and Refinement of SOPs**

To evaluate the possibility that SOPs could exclude informative tests, causing clinically significant diagnoses to be missed, we determined the frequency of discordant tests with positive results. During the entire 18-month analysis period, 4.4% (103/2,341) of discordant tests were positive. Of these, 60% (62/103) were considered redundant—that is, two tests for the same abnormality were both positive (see Materials and Methods). An additional 15% (15/103) were considered likely false-positive tests (see Materials and Methods), positive at low levels in the current bone marrow but negative on previous and/or subsequent samples from the same patient. The remaining discordant positive tests (1.1% of discordant tests) were new MDS-like karyotypic abnormalities or true indicators of minimal residual disease in the absence of positive morphology, both of which may have potential clinical significance.

**Figure 2** Effects of the diagnostic management team (DMT) on test numbers and cost. Regression model (red line) representing the observed (blue dots) weekly number of discordant tests (**A**), omitted tests (**B**), total tests (**C**), and testing costs (**D**) adjusted for the number of specimens during the total 18-month period of analysis (see Materials and Methods). The yellow band indicates the 95% confidence interval for the regression curve. The vertical red line indicates the date of DMT implementation (February 14, 2011).
A significantly higher fraction of concordant than discordant tests was positive (27.1% vs 4.4%; \( P < .001 \)) (Table 3). As a consequence, the fraction of positive tests increased by one-third (17%-23%) from the pre- to postimplementation periods (\( P < .001 \)). Table 4 shows the percentage of positive concordant tests for each combination of diagnosis and clinical scenario. There is considerable variability in these values between different diseases and clinical scenarios. In fact, in several of these combinations (eg, BMF at all stages except post-SCT and myeloma pre-SCT), the positive test rate approached zero.

**Clinicar Response**

The results of the anonymously returned clinician surveys are shown in Table 2. Most agreed or strongly agreed that they trust the pathologist to order appropriate tests and trust the SOPs to recommend the correct tests (questions 1 and 2; 81% and 86%, respectively). Furthermore, given the option, most did not prefer to order ancillary tests themselves (question 3; 63%). Most also agreed that the DMT saves time for the ordering clinician and helps contain costs (questions 4 and 5; 81% and 86%, respectively). The estimated median time savings was 5 minutes per bone marrow procedure, with a range of 2 to 15 minutes. Finally, given the option, most would not prefer to return to clinician-based ordering (question 6; 91%).

**Discussion**

To address the diagnostic challenges faced by clinicians in the era of personalized medicine, we successfully designed and implemented a standardized strategy to guide the selection of cytogenetic and molecular diagnostic tests. The strategy included the development of evidence-based diagnostic algorithms (SOPs) designed by an interdisciplinary team (DMT). SOPs guided test selection throughout each patient’s clinical course, leading to improved evidence-based test selection and more effective test utilization, resulting in estimated annual savings of $522,000 to $1,069,200.

The need for a standardized approach is evidenced by the analysis of pre-DMT ordering patterns, which showed that more than one-third of ordered tests were discordant with evidence- or best practice–based SOPs. Institution of SOP-based ordering procedures led to a significant decrease in discordant (69%) and total (15%) tests and increased the probability of positive results. This higher pretest probability reduces false-positive tests, increasing positive predictive value. In fact, our analysis documented that 15% of discordant positive tests were likely false positives.

The decrease in total tests resulted in significant cost savings to payers. By ensuring that tests are properly ordered in the correct clinical setting, the DMT addresses the need to appropriately reduce health care costs.7,29 When applied nationally, our results predict total annual savings estimated at $191 to $392 million. This value is likely to rise as spending on molecular testing is predicted to markedly increase in coming years.30

Preimplementation analysis also documented omission of recommended tests in many cases, which was markedly reduced (88%) by DMT procedures. These tests are recommended based on their demonstrated utility in facilitating diagnosis, prognosis, monitoring, and therapy. Thus, the inclusion of these previously omitted tests has potential for a positive impact on patient care.

The SOPs were designed using published evidence and guidelines when available. However, for many of the decisions, no evidence or guidelines were available. In those cases, we relied on the experience and judgment of those designing the SOPs. Thus, the possibility that SOPs could exclude informative tests, causing loss of clinically significant data, was a major concern. However, our analysis demonstrated that only 1% of discordant tests provided potentially useful clinical information, indicating that SOPs were nearly always accurate in defining which tests were clinically useful.
An additional benefit of the DMT process is the opportunity for continuous refinement and improvement of SOPs and DMT function. As indicated above, for some testing decisions, there was little or no evidence or consensus from published literature and guidelines. The DMT addresses this deficiency through the continuous collection of testing data, which can then be analyzed to provide evidence needed to further refine the SOPs. For example, Table 4 demonstrates that some tests performed in particular combinations of disease and clinical setting were never or very rarely positive (eg, BMF at diagnosis, follow-up, and pre-SCT or myeloma at pre-SCT), suggesting that these tests may also be unnecessary and could be eliminated with no impact on patient diagnosis.

Ideally, the SOPs could be revised on a regular basis to address these issues as well as to accommodate new tests and other advances in diagnostic standards of care. In this way, the DMT serves as a rapid learning system, a patient-centered approach to health care transformation that uses health information technology to capture diagnostic and outcome data in real-time and in ordinary clinical practice.\(^{31,32}\) These data are rapidly analyzed for new insights that then can be applied to improve subsequent patient care. Through repeated iteration, this allows the system to continuously "learn" better clinical practices. Following this model, with each successive revision, the SOPs would become increasingly accurate and efficient. In addition, this process would help physicians in keeping pace with advances in diagnostic tools.

The success of algorithm-guided diagnostic testing resulted from three factors. First, implementation of standardized, evidence-based guidelines promoted uniform and judicious use of complex cytogenetic and molecular tests. Second, this was a team-based approach encompassing planning, algorithm development, and implementation with collaboration among pathologists, clinical hematologists, and informatics experts, with equal input and responsibility. This promoted trust and communication between clinicians and pathologists, leading to acceptance and utilization. This is evidenced by the increasingly high fraction of bone marrows in which DMT testing was used (Figure 1) and survey data indicating broad acceptance of SOPs and DMT procedures by clinicians (Table 2). Of note, nearly all of the responding clinicians indicated a preference for the DMT procedures over traditional test ordering. This finding is particularly significant since one might expect some clinicians to be hesitant to relinquish control over diagnostic test ordering. Third, DMT procedures delayed the test-ordering decision until after initial morphologic and flow cytometric examination of the bone marrow aspirate (see Materials and Methods). This narrowed the differential diagnosis and allowed more accurate categorization of disease and clinical status prior to test selection. Similar elements were described as key predictors of success in other reports on the use of clinical decision support.\(^8\)

It is important to note that participation in the DMT was optional. For each bone marrow specimen, clinicians were allowed to choose between DMT testing and traditional non-DMT ordering. This decision was made for two reasons. First, while the SOPs were designed to be as comprehensive as possible, we recognized that they could not cover every conceivable clinical situation and that there would be situations when clinicians need to order tests “off protocol” for best patient care. Second, since teamwork was an important element of the DMT, we believed that there would be broader acceptance if SOPs were not mandated. The high utilization rate and positive clinician survey data appear to support this decision.

One limitation to our study is the lack of concurrent controls or randomized assignment to the DMT utilization. A second limitation is the lack of patient outcome and long-term follow-up data. Efforts to access the impact of our changes on patient survival and quality of life are ongoing. Finally, the analyses were based on the ordering practices and payer characteristics at Vanderbilt University. While it is likely that these practices are common throughout the country, the impact of DMT procedures may vary by location.

The DMT serves as a model for optimizing complex diagnostic testing—a model that improves quality and reduces the cost of care. This report describes the development and implementation of evidence-based testing algorithms that were facilitated by a team approach to diagnosis and management of hematologic malignancies. It demonstrates that such an approach can improve test utilization, reducing unnecessary tests and ensuring the correct tests are ordered for each patient. In the process, costs are reduced and the probability that testing will produce clinically useful information is increased. This approach also improves communication between the pathologists and oncologists and allows oncologists to spend more time treating patients rather than ordering tests. The effort described here was focused on hematologic malignancies; however, the application of this process is broadly applicable in a wide range of clinical scenarios. The data presented here confirm the role of the DMT approach in supporting the expansion of affordable, personalized medicine.

Address reprint requests to Dr Zutter: Deps of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Room C-3321A, 1161 21st Ave S, Nashville, TN 37232-2561; mary.zutter@vanderbilt.edu.

Support: The REDCap database tool is maintained by the Vanderbilt Institute for Clinical and Translational Research, supported by grant UL1TR000011 from the National Center for Advancing Translational Sciences/National Institutes of Health. Disclosures: Dr Stead is director of HealthStream and coinventor of two medical record products—one licensed to McKesson and one licensed to Informatics Corporation of America—from which he receives royalties through Vanderbilt University.
Acknowledgments: We gratefully acknowledge the contributions of Leslie Goebel and Carey Clifton, who provided invaluable insight into clinical workflow and assisted in the application of the DMT into clinical practice. We also thank Brenda Jarvis for assistance with data entry and database support.

References