The Efficacy of T2 Magnetic Resonance Assay in Monitoring Candidemia after the Initiation of Antifungal Therapy: The Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) trial

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Running title: T2MR for monitoring candidemia clearance

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Abstract

The performance of blood culture in monitoring candidemia clearance is hampered by its low sensitivity, especially during antifungal therapy. T2 Magnetic Resonance (T2MR) assay combines magnetic resonance with nanotechnology to identify whole Candida spp. cells. A multicenter clinical trial studied the performance of T2MR in monitoring candidemia clearance compared to blood culture. Adults with a blood culture positive for yeast were enrolled and had blood cultures and T2MR testing on prespecified days. Thirty-one patients completed the trial. Thirteen of the 31 patients (41.9%) had at least one positive surveillance T2MR and/or blood culture. All positive blood cultures (7/7; 100%) had an accompanying positive T2MR result with concordance in the identified Candida spp., while only 7/23 (30.4%) T2MR results had an accompanying positive blood culture. There was one case of discordance in species identification between T2MR and the pre-enrollment blood culture with evidence to support deep-seated infection by the Candida spp detected by T2MR. Based on the log-rank test, there was a statistically significant improvement of post-treatment surveillance using the T2MR compared to blood culture (p=0.004). Limitations of the study include the small sample size and lack of outcomes data. In conclusion, T2MR significantly outperformed blood cultures in monitoring the clearance of candidemia in patients receiving antifungal therapy, and may be useful in determining adequate source control, timing for de-escalation and optimal duration of treatment. However, further studies are needed to determine the viability of Candida spp. cells detected by the T2MR and correlate the results with patient outcomes.
Introduction

Invasive candidiasis is a healthcare-associated infection with high morbidity and mortality that exceeds 40% (1-3). Optimal antifungal therapy and control of the source of infection constitute the cornerstones for successful treatment (4, 5). As part of optimal antifungal therapy, the most recent Infectious Diseases Society of America (IDSA) clinical practice guidelines support follow-up blood cultures every 24-48h in order to monitor clearance of candidemia, determine the need for further interventions for source control, and guide de-escalation as well as total duration of therapy (6). However, the low sensitivity, the suppression by antifungal therapy and the prolonged time to result (3-5 days) deem blood cultures a suboptimal tool to guide treatment of candidemia.

More specifically, despite the reliance on blood culture as a monitoring standard to guide therapy, blood cultures perform poorly in detecting invasive candidiasis. In studies comparing their performance with post-mortem autopsy results of patients proven to have invasive candidiasis, sensitivity of blood cultures ranged from 21-71% (7). Moreover, blood cultures are heavily influenced by the initiation of antifungal therapy. For example, in a study examining the performance of two commonly used blood culture systems in seeded blood culture bottles, the addition of therapeutic levels of antifungal agents halved the detection rate of Candida spp. (8, 9). Even fungal-specific blood cultures have not been shown to outperform regular blood cultures in clinical trials (10-12), they are rarely used in clinical practice and are not included in the recently published guidelines for monitoring of candidemia.

The T2 Magnetic Resonance technology platform (T2MR) combines magnetic resonance with nanotechnology to identify whole Candida cells within 3-5 hours of
processing a sample (8, 13). T2MR directly analyzes whole blood specimens to identify
Candida spp. without the need for prior isolation of Candida cells with a specificity of
99.4% and sensitivity of 91.1% (14). Importantly, early in vitro interference studies for
exogenous substances have shown that T2MR assay is not suppressed by the presence of
antifungal agents (8, 15). The purpose of this multicenter prospective clinical trial,
designated the Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) trial,
was to investigate the performance of T2MR assay as a monitoring tool for post-therapy
clearance of candidemia compared to blood cultures.
Results

Overall, 188 patients were screened, of whom 42 patients met the inclusion criteria and consented to participate in the clinical trial. Among those, 6 patients had either inadequate number of samples collected or samples were collected outside the prespecified window, 3 patients had blood cultures with Candida spp. other than the 5 detected by T2MR (1 Candida lusitaniae, 1 Candida guilliermondii and 1 Candida dubliniensis), 1 withdrew from the study and 1 eventually grew Trichosporon asahii, initially identified as yeast on the pre-enrollment blood culture, and were excluded from the study (Figure 2, Flow Chart). Thirty-one patients completed the study and their data were used for the study analysis. All patients had a single Candida spp. isolated from their pre-enrollment blood culture, except for 1 with both C. albicans and C. parapsilosis.

The frequency of isolated Candida spp. among the 31 patients was C. glabrata (12/31; 38.7%), C. albicans (11/31; 35.5%), C. tropicalis (4/31; 12.9%), C. parapsilosis (2/31; 6.5%), C. krusei (1/31; 3.2%) and C. albicans/C. parapsilosis (1/31; 3.2%) (Table 1).

In 18 patients (58.1%), all surveillance T2MR specimens and blood cultures collected for the purposes of the study were negative. Patient data for the remaining 13 patients (41.9%), who had at least one positive surveillance blood culture or T2MR test, are outlined in Table 1. In total, out of the 93 sets of blood cultures and T2MR specimens that were collected, 7 blood cultures (7.5%) vs. 23 T2MR specimens (24.7%) were positive (p=0.001) in 4 (12.9%) and 13 (41.9%) unique patients respectively (p=0.01) (Table 1). Of note, all positive surveillance blood cultures had a positive accompanying T2MR result with concordance in the identified Candida spp. (7/7, 100%), compared to only 7/23 (30.4%) positive T2MR results with an accompanying positive blood culture.
In 4 out of 13 patients T2MR and blood cultures were not collected on at least one of the prespecified study visits (on one visit in Patients 5, 8 and 11 and on two visits in Patient 13). This was due to visits falling on holiday weekends or due to device malfunction. In Patient 3 T2MR assay was invalid on Day 7 on both Tubes A and B.

By the end of the first surveillance week, candidemia was still detected in 18.2% of patients (2/11) by the T2MR (Patients 2 and 4) vs. 0% by the blood cultures. The Kaplan-Meier curves showing the length of time that the 31 patients remained candidemic by the 2 diagnostic methods are presented in Figure 3. Based on the log-rank hypothesis, which was used to compare the time to negative result distributions for the 2 surveillance methods, there was a statistically significant improvement of post-treatment surveillance using the T2MR test compared to the regular blood cultures (chi-square of 8.2, p=0.004) (Figure 3).

Given the intermittent presence of Candida spp. cells in the blood in patients with invasive candidiasis, we reviewed the data of the patients with positive T2MR results to analyze the frequency of detection of patients with ongoing infection during each one of the sampling days (Table 1). Among the total of 13 patients with positive T2MR results during the study, 9 had a positive result on day 0 (Table 1). The addition of a second blood draw on day 3 allowed the detection of 3 more patients with ongoing infection who had negative T2MR on day 0 (Patients 1, 9 and 13), increasing the detection rate by 33.3%. On day 5, another patient with active infection but negative prior specimens was identified (Patient 10), but that patient had a different Candida spp. (C. albicans) from the pre-enrollment blood culture (C. glabrata) with evidence to suggest that this represented a new deep-seated infection, with C. albicans isolated from biloma drainage.
culture. Sampling on day 7 did not identify any patients that were not already positive on previous blood draws.
Even though clinical practice guidelines support follow-up cultures in order to monitor clearance of candidemia and guide therapy (6), blood cultures are a suboptimal tool to guide treatment of candidemia. In the STAMP trial, we studied the performance of the T2MR assay as a monitoring tool for mycologic response to antifungal therapy in patients with candidemia. We followed 31 candidemic patients during their treatment with antifungal agents. All positive surveillance blood cultures had an accompanying positive T2MR result with concordance in the identified Candida spp., while only 7/23 (30.4%) T2MR results had an accompanying positive blood culture. Interestingly, we found a statistically significant improvement of post-treatment surveillance using the T2MR test compared to the regular blood cultures based on the Kaplan-Meir curves, with 18.2% of patients (2/11) remaining candidemic by the end of the first surveillance week based on the T2MR compared to none based on the blood cultures. All T2MR results were in agreement in terms of speciation both with the paired and the pre-enrollment blood cultures, except for one patient (Patient 10) where the T2MR sample on day 5 was positive for a different Candida spp. compared to the pre-enrollment blood culture with evidence to support deep-seated infection from this species.

This study provides evidence that T2MR might outperform blood cultures in monitoring the clearance of Candida spp. in candidemic patients who are on antifungal treatment. This could be at least partially explained by the fact that T2MR results are not suppressed by antifungal agents. Indeed, published studies have demonstrated a decrease in the performance of blood cultures in detecting candidemia in the presence of therapeutic levels of antifungal agents (9). While T2MR detects whole cells and not
cell fragments or free DNA, *in vitro* studies suggested that the result is not inhibited by antifungal agents (8). This observation was also supported in the current clinical trial by the fact that none of the 31 patients who were on antifungal treatment had persistently invalid T2MR results that, as explained in the methods, would indicate the potential inhibition of T2MR by the presence of therapeutic levels of antifungal agents.

Another factor that may have contributed to the significantly improved performance of T2MR could be the long time to positivity for specific *Candida* spp., such as *C. glabrata*, that frequently exceeds the typical 5-day period that cultures are processed (16, 17). This becomes particularly important as, in an expanding number of clinical centers, non-*albicans* spp. represent >50% of clinical isolates (18). Indeed, in this trial, *C. glabrata* was detected in almost 39% of patients (12/31), and was the most frequent isolate among the enrolled patients. All subsequent surveillance blood cultures of those patients were negative, in comparison to 5 positive surveillance T2MR results in 3 different patients (Patients 1, 6 and 11).

The 2016 IDSA guidelines recommend empiric treatment with an intravenous echinocandin and subsequent transitioning to oral fluconazole as soon as surveillance cultures are negative (for patients that are clinically stable and with a fluconazole-susceptible isolate). Based on studies using data from autopsy proven cases of invasive candidiasis, we know that the sensitivity of blood cultures for diagnosing invasive candidiasis is roughly 50%, in a large part because of the intermittent nature of candidemia in deep-seated infections (7). In this study, a requirement of two consecutive negative T2MR results to document clearance of *Candida* from the bloodstream increased the possibility of detecting ongoing fungemia by 33.3%. This
seems to indicate that more than one T2MR results would be needed to demonstrate candidemia clearance. However, future clinical trials with collection of surveillance samples for longer periods are needed to validate the above and determine the required number of negative results that would be enough to justify mycologic response to therapy.

The rapid turn-around time of T2MR (mean time to negative result of 4.2 ± 0.9 hours and to species identification of 4.4 ± 1.0 hours (14)) compared to the 5 days that blood cultures take to finalize, can hasten adjustment of antifungal therapy by 3 days even when requiring 2 consecutively negative T2MR results within 48h and 1 negative blood culture to document clearance. Echinocandins, the recommended first line treatment for candidemia, are generally well-tolerated (19, 20). The de-escalation to another class of antifungals can reduce the risk of resistance development, since echinocandin resistance is almost always associated with previous exposure and prolong treatment courses (21). The faster transition to oral therapy would also be expected to have implications in reducing hospital costs by reducing length of stay among others (22).

Additionally, the rapid turn-around time of T2MR could allow for timely adjustment of the treatment plan. Mortality in candidemia is closely linked to source control with mortality rates approaching 100% in patients with septic shock without timely source control (4). Central venous catheters are not always the source of infection (6). Persistently positive T2MR results in patients with central venous catheter (CVC) may, however, be the determining factor in a decision to remove a CVC. Further, consistently positive results in a patient after CVC removal may point to
deep-seated infection and alert the clinician on the need for additional diagnostic work-up to rule out visceral candidiasis. Indeed, in our study we observed one patient with a positive T2MR result 5 days after enrollment, following 2 negative surveillance T2MR specimens, and this correlated with the diagnosis of *Candida* biloma (Patient 10). Even though in this case, the bile drainage culture was already finalized positive for *C. albicans* 2 days prior to the collection of the T2MR sample, this finding indicates that T2MR can detect deep-seated candidiasis and potentially guide treatment decisions in cases where deep culture data are not available.

It should be noted that using T2MR for monitoring of candidemia is limited by the ability to recognize only 5 *Candida* spp. This is particularly important in the era of increasing prevalence of other *Candida* spp., especially *Candida auris*, worldwide. However, based on worldwide registry data, over 92% of invasive disease is still caused by the 5 *Candida* spp. detected by the T2MR assay (23). Indeed, out of the 43 patients who were consented to participate in the study, only 3 (7%) were excluded due to isolation of *Candida* spp. other than the ones detected by T2MR. Another potential shortcoming of the assay is that T2MR may detect non-viable whole *Candida* cells after initiation of antifungal therapy. This could potentially explain the intermittent positive T2MR results (i.e. Patients 2 and 4). Furthermore, the intermittent release of *Candida* cells into the blood of patients with deep-seated candidiasis or the different *Candida* burden during the disease course, would be another plausible explanation, but further studies are needed to justify the above. Weakness of the study include the small sample size and the fact that we did not use T2MR results to guide clinical decision-making, so as to correlate the results with patient outcomes. Thus, it is uncertain
whether incorporating T2MR monitoring into clinical practice for the management of

known candidemia leads to improved clinical outcomes and a decrease in the duration

of intravenous antifungal treatment, as well as side effects from antifungals and

emergence of resistant *Candida* spp. is to be shown in future studies. Furthermore,

despite some evidence in this study that T2MR might be able to detect at least some

cases of deep-seated candidiasis, future studies are needed to determine the

performance of T2MR in invasive candidiasis without candidemia. The above should

be addressed in well-designed clinical trials which will incorporate T2MR monitoring

into critical management decisions among patients with proven and suspected

candidemia.

The incorporation of T2MR assay in daily practice is anticipated to pose financial

challenges in the hospital budget (24, 25). Bilir *et al.* studied the economic impact of

incorporating T2MR in diagnostic protocols in certain high-risk patient populations with

a 3% prevalence of disease, such as critical care admissions, solid organ transplantation,

hematopoietic stem cell transplantation and oncology patients (26). The diagnostic

strategy that incorporated T2MR, was estimated to result in potential annual savings of

$5,858,448 and a 47.6% reduction of cost in a 500-bed hospital, with the savings mostly

driven by a reduction in mortality and days of hospital stay.

In conclusion, the finding of this clinical trial that almost one third of patients had

ongoing fungemia after the first negative blood culture indicates the need to revisit the

way we currently determine duration of therapy starting from the first negative blood

culture. The STAMP trial provides strong evidence that, among patients on antifungal

therapy, T2MR can be used to detect ongoing candidemia timelier than the traditionally
used blood cultures. T2MR has the potential to be a monitoring tool for patients with invasive candidiasis and, given its quick turnaround, may provide “actionable information” to adjust treatment.
Methods

T2 Magnetic Resonance Assay

T2MR is a qualitative assay that utilizes the magnetic resonance based approach used in MRI technology and is run automatically on the T2Dx instrument. Details about this technology can be found in (8). In brief, T2Dx lyses Candida cells by mechanical bead beating, uses pan-Candida PCR primers to amplify the intervening transcribed spacer 2 (ITS2) region within the Candida ribosomal DNA operon, introduces superparamagnetic nanoparticles coated with binding agents that target species-specific capture probes nested within the pan-Candida amplicons into whole blood samples, and, finally, detects and “speciates” amplified product by measuring the magnetic resonance signal produced as the result of the agglomeration of the superparamagnetic particles. The T2MR assay has been designed to detect intact Candida cells and not circulating DNA due to the unclear clinical relevance of circulating pathogen DNA as a marker of infection (8).

In order to monitor for the presence of inhibitors, T2MR processes an internal control with each clinical specimen. If the internal control is invalid and there are no positive T2MR signals, an “invalid” result is displayed, indicating the possible existence of an inhibitor that interferes with Candida detection. T2MR assay is designed to detect 5 Candida spp.: Candida albicans, Candida tropicalis, Candida krusei, Candida glabrata and Candida parapsilosis. T2MR results are grouped and 3 results are reported: C. albicans/C. tropicalis, C. krusei/C. glabrata, and C. parapsilosis on the basis of antifungal resistance patterns of the aforementioned Candida spp. (6).
 Trial Design

The STAMP clinical trial was conducted between September 2014 and April 2017 at 3261 centers in the United States. Patients aged 18–95 years with a blood culture positive for yeast receiving or scheduled to receive antifungal therapy within 12h from the positive blood culture result were eligible for participation in the study. Patients had to be enrolled within 36h from the positive blood culture result. Patients receiving any novel drug compound within 30 days prior to potential enrollment were excluded from the study. In cases where the yeast identified in the pre-enrollment blood culture was different from the 5 Candida spp. targeted by the T2MR technology, patients were withdrawn from the study and no further blood draws were performed. The institutional review board of each center approved the study protocol. Written informed consent was obtained from all patients (ClinicalTrials.gov identifier: NCT02163889).

Sample Collection and Outcomes

A set of aerobic and anaerobic blood cultures and 3 whole blood T2MR specimens (Tubes A, B and C) were collected from each participant on the day of enrollment (day 0) and then on days 3, 5 and 7 or until hospital discharge (Figure 1). Only the data of patients who had at least 2 surveillance sets of T2MR specimens and blood cultures collected were used in the study analysis. A window of 1 day was allowed for study visits to account for weekends and holidays. Patients who were discharged before having 2 specimens collected were excluded from the study. T2MR results were not used for clinical decision making and the antifungal regimen was determined in accordance with routine institutional practice.
T2MR specimens and blood cultures were collected at the same time from the same anatomical collection site either through a peripheral venipuncture or from a central line or port. T2MR clinical specimens were collected in K2 ethylenediaminetetraacetic acid (EDTA) plastic blood collection vacutainers. Tube A was stored at room temperature (20°C–25°C) and was analyzed within 12 hours of collection. Tube B was refrigerated up to 72h until Tube A was successfully run and was then frozen if not tested. Tube C was maintained in frozen storage (−70°C to −80°C) immediately after collection. Blood cultures were processed in accordance with routine institutional practice for a period of 5 days or until a positive blood culture result was reported, whichever occurred first. The BacT/Alert 3D, BacTec FX and Versatrek blood culture systems were used in the participating study centers. In cases of positive blood cultures, the species of the blood stream isolate was identified with MALDI-TOF, Vitek 2, Microscan or PNA probe, in accordance with routine institutional practice.

Statistical Analysis

The collected data were represented as lifetime data, and the Kaplan-Meier estimator was used to measure the length of time patients remained candidemic on the 2 diagnostic methods. A log-rank test was used to compare the above distributions of the two samples. Categorical data were presented as relative frequencies and were compared with the chi-squared test. Statistical significance was set at 0.05. Statistical analysis was performed using the Stata v14 software package (Stata Corporation, College Station, TX, USA).
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Figure Legends:

Figure 1: Graphic Representation of Study Design
Figure 2: Flow Chart
Figure 3: Kaplan-Meier Diagram for the First Week of Surveillance
# Table 1: Baseline Characteristics of Study Participants with Positive Surveillance T2MR and/or Blood Culture and Individual T2MR and Blood Culture Results for Subjects with at least 1 Positive Surveillance Test over the First Week of Monitoring.

| Study ID | Age | Acute medical condition | Patient Location | Time of enrollment from day of positive culture | Antifungal therapy prior to enrollment | Central line/Port at the time of enrollment | Candida spp. in pre-enrollment blood culture; time to species identification | Time of removal of central lines | Anti-fungal therapy during study enrollment | Day 0* T2MR result | Day 0* Blood culture result | Day 3* T2MR result | Day 3* Blood culture result | Day 5* T2MR result | Day 5* Blood culture result | Day 7* T2MR result | Day 7* Blood culture result |
|----------|-----|--------------------------|------------------|-----------------------------------------------|--------------------------------------|------------------------------------------|-----------------------------------------------|---------------------------------|----------------------------------|-----------------|-----------------------------|-----------------|-----------------------------|-----------------|-----------------------------|-----------------|-----------------------------|
| 1        | 42  | Abdominal surgery        | MICU             | 20h                                           | FLX started on day of positive culture | Yes C. glabrata 6d; Between days 3-5* | FLX changed to MFG on day 3*                  | Negative                        | Negative                        | Positive K/G    | Negative                     | Negative         | Negative                     | Negative         | Negative                     | Negative         | Negative                     |
| 2        | 56  | CV disease, IDDM, Renal insufficiency | CCU             | 8h                                           | MFG started on day of positive culture | Yes C. tropicalis 3d; Between days 0-3* | MFG changed to FLX on day 2*                  | Positive A/T; Negative            | Negative                        | Negative         | Negative                     | Negative         | Negative                     | Positive         | Negative                     | Negative         | Negative                     |
| 3        | 51  | Colon cancer             | Medical ward     | 28h                                           | MFG started on day of positive culture | Yes C. albicans 4d; Between days 0-3* | MFG changed to FLX on day 3*                  | Positive A/T; Positive A          | Negative                        | Positive         | Negative                     | Negative         | Negative                     | Negative         | Negative                     | Negative         | Negative                     |
| 4        | 23  | Severe burns, Abdominal surgery, Severe neutropenia | MICU             | 26h                                           | MFG started on day of positive culture | Yes C. tropicalis 3d; Between days 0-3* | MFG changed to FLX on day 3*                  | Positive A/T; Negative            | Negative                        | Positive         | Negative                     | Negative         | Negative                     | Positive         | Negative                     | Negative         | Negative                     |
| 5        | 54  | Bowel transplant, On steroid tx, TPN dependent | SICU             | 28h                                           | FLX started on day of positive culture and was changed to CAS the following day | Yes C. tropicalis 5d; Between days 0-5* | CAS                                          | Positive A/T; Positive T          | Not done                        | Not done                    | Negative                     | Negative         | Negative                     | Negative         | Negative                     | Negative         | Negative                     |
| No. | Case | Disease/Procedure | Unit | LOS (h) | Infections | Infection Details | Antifungal Therapy | Bloodstream Infection Details | Outcome |
|-----|------|-------------------|------|---------|------------|------------------|-------------------|--------------------------|---------|
| 6   | 66   | Pancreatic cancer, Abdominal surgery, Mild neutropenia | Surgical Oncology | 5d 6h** | CAS started on the 3rd day after positive culture | Yeast | C. glabrata, 14d | Between days 0-3** | CAS changed to FLC on day 5* | Positive K/G | Negative | Positive K/G | Negative | Negative | Negative | Negative | Negative | Negative |
| 7   | 35   | CV disease, IVDDU, Cardiology | 9h | CAS started on day of positive culture | Yeast | C. parapsilosis, 2d | No central line in place at the time of study enrollment | CAS changed to FLC on day 2* and FLC to LAB on day 3* | Positive P | Positive P | Positive P | Positive P | Negative | Negative | Negative | Negative | Negative |
| 8   | 42   | FAP, Abdominal surgery | SICU | CAS started on day of positive culture | Yeast | C. albicans, 5d | Between days 0-3* | FLC | Positive A/T | Positive A | Negative | Negative | Not done | Not done | Negative | Negative | Negative |
| 9   | 47   | Sickle cell disease, CV disease | Medical ward | CAS started on the 1st day after positive culture | Yeast | C. albicans, 1d | Not removed | FLC | Negative | Negative | Positive A/T | Negative | Negative | Negative | Negative | Negative | Negative |
| 10  | 51   | CV disease, Abdominal surgery | Medical ward | VCZ started on the 3rd day after positive culture | Yeast | C. glabrata, 2h | No central line in place at the time of study enrollment | VCZ changed to CAS on day 5* | Negative | Negative | Negative | Negative | Negative | Positive A/T | Negative | Negative | Negative |
| 11  | 58   | CV disease, IDDM, Spinal surgery | Medical ward | FLC started 2 days prior to positive culture | Yeast | C. glabrata, 15h | CAS | Positive K/G | Negative | Not done | Not done | Negative | Negative | Negative | Negative | Negative | Negative |
| 12  | 28   | Brain tumor, CV disease | Medical ward | CAS started on day of positive culture | Yeast | C. albicans, 6h | Between days 0-3* | CAS changed to LAB on day 1* | Positive A/T | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| 13  | 25   | Not available | Medical ward | CAS started on day of positive culture | Yeast | C. albicans, 12h | Not removed | CAS | Negative | Negative | Positive A/T | Negative | Not collected | Not collected | Not collected | Not collected | Not collected |
Footnote: CAS: Caspofungin, CCU: Coronary Care Unit, CV: Cardiovascular, d: days, F: Female, FLC: Fluconazole, h: hours, IDDM: Insulin Dependent Diabetes Mellitus, LAB: Liposomal Amphotericin B, M: Male, MICU: Medical Intensive Care Unit, MFG: Micafungin, NA: Non Applicable, SICU: Surgical Intensive Care Unit, TPN: Total Parenteral Nutrition, Tx: therapy, VCZ: Voriconazole. *Days are defined from study enrollment, **Protocol deviation regarding timing of study enrollment, †Day 3 visit was not performed, ‡Time from culture positivity for yeast to species identification, ∆Samples were collected within +1 day window from the prespecified study visit to account for weekends and holidays, ††Samples were collected within -1 day window from the prespecified study visit to account for weekends and holidays.
Blood culture result is one of the 5 Candida species targeted by the T2MR technology (C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei).

Patient has to be enrolled within 36 hours of blood culture result.

*Patient should receive antifungal therapy within 12 hours of positive blood culture.

A set of blood cultures and 3 T2MR specimens are collected at the same time and from the same anatomic location.

Figure 1: Graphic Representation of Study Design
188 patients were screened

146 patients failed the screening

11 patients consented but withdrew from the study

31 patients completed the study

- 6 had inadequate number of samples collected or samples collected outside the prespecified window
- 3 had isolated organisms other than the 5 Candida spp. detected by T2MR
- 1 grew Trichosporon asahii on pre-enrollment blood culture
- 1 patient withdrew consent

Figure 2: Flow Chart
Time to negative result

chi2 = 8.17
p = 0.0042

Figure 3: Kaplan-Meier Diagram for the First Week of Surveillance