T2 Biosystems, Inc.
Form 10-K
March 04, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the year ended December 31, 2014

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission File Number: 001-36571

T2 Biosystems, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-4827488**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
101 Hartwell Avenue, Lexington, MA	**02421**
(Address of principal executive offices)	(Zip code)

Registrant s telephone number, including area code: **781-457-1200**

Securities registered pursuant to Section 12(b) of the Act

Title of Each Class:	**Name of Each Exchange on which Registered:**
Common Stock, par value $0.001 per share	**The NASDAQ Stock Market LLC**
	(NASDAQ Global Market)

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act of 1933, as amended. YES o NO x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended. YES o NO x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

Large accelerated filer o Accelerated filer o Non-accelerated filer x Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No x

As of June 30, 2014, the last business day of the registrant s most recently completed second fiscal quarter, the registrant s common stock was not listed for trading on any exchange or over-the-counter market and there was no established public market for the common stock. The common stock began trading on The NASDAQ Global Market on August 7, 2014. As of December 31, 2014, the aggregate market value of the registrant s common stock held by non-affiliates was approximately $170.7 million based on the closing price for the common stock of $19.24 on that date. Shares of common stock held by each executive officer, director, and their affiliated stockholders have been excluded from this calculation as such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of outstanding shares of the registrant s common stock on March 2, 2015 was 20,125,635. The common stock is listed on the NASDAQ Global Market (trading symbol TTOO).

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive Proxy Statement to be filed with the Securities and Exchange Commission within 120 days after the close of the fiscal year are incorporated by reference into Part III of this report.

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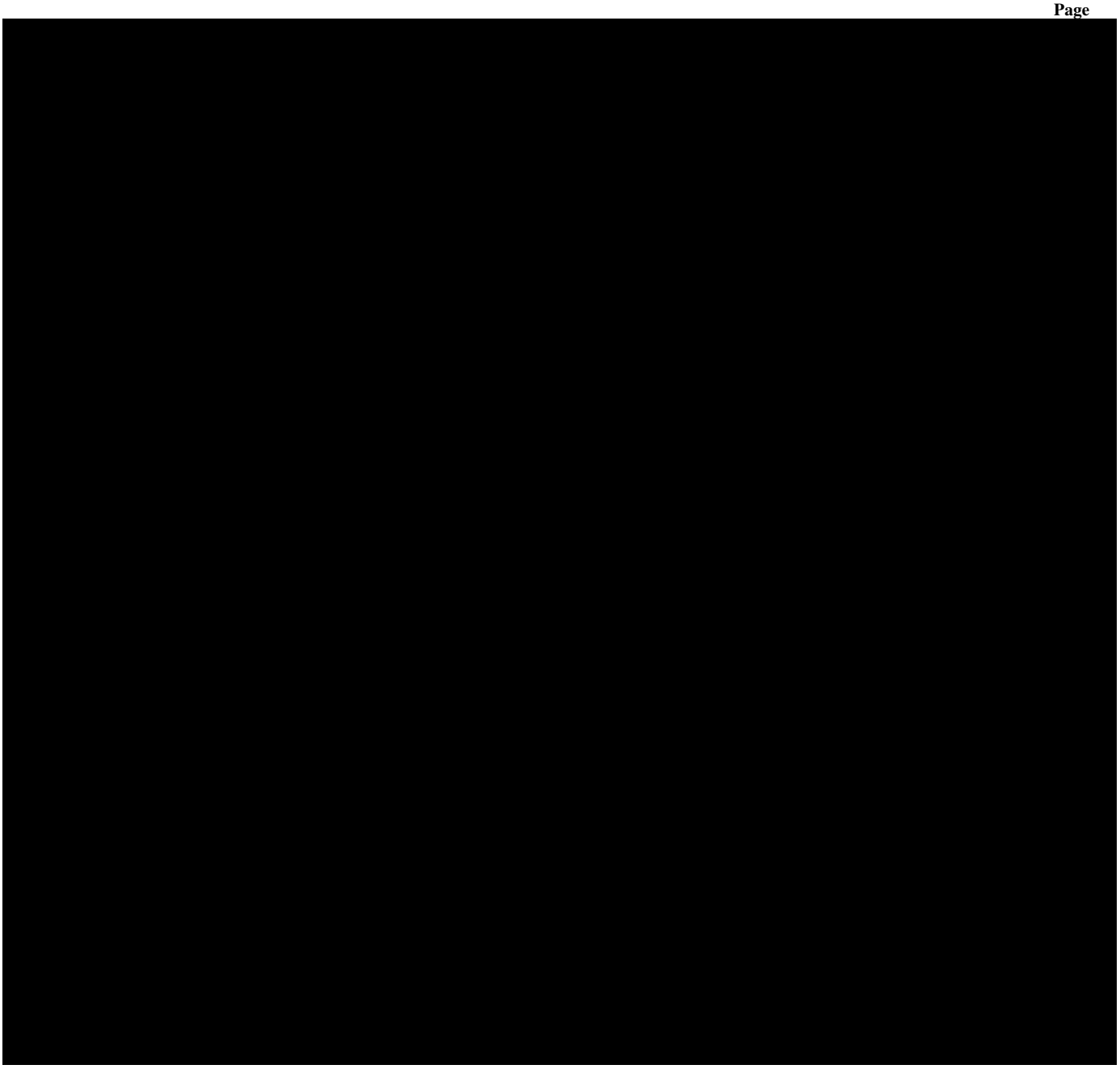

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements about us and our industry that involve substantial risks and uncertainties. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, or the Exchange Act. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy, prospective products and product candidates, their expected performance and impact on healthcare costs, marketing authorization from the U.S. Food and Drug Administration, or FDA, regulatory clearance, reimbursement for our product candidates, research and development costs, timing of regulatory filings, timing and likelihood of success, plans and objectives of management for future operations and future results of anticipated products, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

In some cases, you can identify forward-looking statements by terms such as may, will, should, expect, plan, anticipate, could, intend, target, project, contemplate, believe, estimate, predict, potential or continue or the negative of these terms or other similar expressions. The forward-looking statements in this Annual Report on Form 10-K are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Annual Report on Form 10-K and are subject to a number of risks, uncertainties and assumptions described under the sections in this Annual Report on Form 10-K entitled Item 1A. Risk Factors . These forward looking statements are subject to numerous risks, including, without limitation, the following:

- *our expectation to incur losses in the future;*
- *our ability to obtain marketing authorization from the FDA or regulatory clearance for new product candidates in the United States or any other jurisdiction;*
- *the market acceptance of our T2MR technology;*
- *our ability to timely and successfully develop and commercialize our existing products and future product candidates;*
- *the length of our anticipated sales cycle;*
- *our ability to gain the support of leading hospitals and key thought leaders and publish the results of our clinical trials in peer-reviewed journals;*

- *our future capital needs and our need to raise additional funds;*

- *the performance of our diagnostics;*

- *our ability to successfully manage our growth;*

- *our ability to compete in the highly competitive diagnostics market;*

- *our ability to protect and enforce our intellectual property rights, including our trade secret-protected proprietary rights in T2MR; and*

- *federal, state, and foreign regulatory requirements, including FDA regulation of our product candidates.*

These forward-looking statements represent our estimates and assumptions only as of the date of this Annual Report on Form 10-K. Unless required by U.S. federal securities laws, we do not intend to update any of these forward-looking statements to reflect circumstances or events that occur after the statement is made or to conform these statements to actual results. The following discussion should be read in conjunction with the financial statements and notes thereto appearing elsewhere in this Annual Report on Form 10-K. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of various factors.

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes thereto included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the Item 1A. Risk Factors section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

PART I.

Item 1. BUSINESS

Overview

We are an *in vitro* diagnostics company that has developed an innovative and proprietary technology platform that offers a rapid, sensitive and simple alternative to existing diagnostic methodologies. We are using our T2 Magnetic Resonance platform, or T2MR, to develop a broad set of applications aimed at lowering mortality rates, improving patient outcomes and reducing the cost of healthcare by helping medical professionals make targeted treatment decisions earlier. T2MR enables rapid detection of pathogens, biomarkers and other abnormalities in a variety of unpurified patient sample types, including whole blood, plasma, serum, saliva, sputum and urine, and can detect cellular targets at limits of detection as low as one colony forming unit per milliliter, or CFU/mL. Our initial development efforts utilizing T2MR target sepsis, hemostasis, and Lyme disease, which are areas of significant unmet medical need in which existing therapies could be more effective with improved diagnostics.

On September 22, 2014, we received market authorization from the U.S. Food and Drug Administration, or the FDA, for our first two products, the T2Dx Instrument and the T2Candida Panel, which have the ability to rapidly identify the five clinically relevant species of *Candida*, a fungal pathogen known to cause sepsis. We began the process to commercialize these products in the fourth quarter of 2014 and anticipate our first sales in 2015.

Our next three diagnostic applications are called T2Bacteria, T2HemoStat, and T2Lyme, which are focused on bacterial sepsis infections, hemostasis, and Lyme disease, respectively. We plan to initiate clinical trials in the second half of 2015 for T2Bacteria and in 2016 for T2HemoStat. We expect that existing reimbursement codes will support our sepsis, hemostasis and Lyme disease product candidates, and that the anticipated economic savings associated with our sepsis products will be realized directly by hospitals.

Sepsis is one of the leading causes of death in the United States and the most expensive hospital-treated condition. Most commonly afflicting immunocompromised, critical care and elderly patients, sepsis is a severe inflammatory response to a bacterial or fungal infection with a mortality rate of approximately 30%. According to data published by the U.S. Department of Health and Human Services for 2011, the cost of sepsis is over $20 billion in the United States, or approximately 5% of the total aggregate costs associated with domestic hospital stays. Sepsis is typically caused by one or more of five *Candida* species or over 25 bacterial pathogens, and effective treatment requires the early detection and identification of these specific target pathogens in a patient s bloodstream. Today, sepsis is typically diagnosed through a series of blood cultures followed by post-blood culture species identification. This method has substantial diagnostic limitations that lead to a delay of up to several days in administration of targeted treatment and the incurrence of unnecessary hospital expense. Without the ability to rapidly identify pathogens, physicians typically start treatment of at-risk patients with broad-spectrum antibiotics, which can be ineffective and unnecessary and have contributed to the spread of antimicrobial resistance. According to a study published by *Critical Care Medicine* in 2006, in sepsis patients with documented hypotension, administration of effective antimicrobial therapy within the first hour of detection was associated with a survival rate of 79.9% and, over the ensuing six hours, each hour of delay in initiation of treatment was associated with an average decrease in survival of 7.6%.

We believe our sepsis products will redefine the standard of care in sepsis management while lowering healthcare costs by improving both the precision and the speed of detection of sepsis-causing pathogens. According to a study published in the *Journal of Clinical Microbiology* in 2010, targeted therapy for patients with bloodstream infections can be delayed up to 72 hours due to the wait time for blood culture results, leading to the conclusion that more-rapid identification of the causative organism would be highly desirable to facilitate targeted treatment in the critical phase of septic illness. In another study published in *Clinical Infectious Diseases* in 2012, the delayed administration of appropriate anti-fungal therapy was associated with higher mortality among patients with septic shock attributed to *Candida* infection and, on that basis, the study stated that more rapid and accurate diagnostic techniques appear to be needed. Our pivotal clinical trial demonstrated that T2Candida can deliver actionable results as fast as three hours, with an average time to result during the trial of 4.2 hours, rather than the two to five or more days typically required for blood-culture-based diagnostics, which we believe will enable physicians to make treatment decisions and administer targeted treatment to patients on an accelerated basis. We believe that T2Bacteria will also deliver actionable results within these timeframes because this diagnostic panel is designed to run on the same instrument as T2Candida.

Candida has an average mortality rate of approximately 40%, and according to a study published in *Antimicrobial Agents and Chemotherapy* in 2010, this mortality rate can be reduced to 11% with the initiation of targeted therapy within 12 hours of presentation of symptoms. In a study published in the *American Journal of Respiratory and Critical Care Medicine* in 2009, providing targeted antifungal therapy within 24 hours of the presentation of symptoms decreased the average cost of care by approximately $30,000 per patient. We expect the anticipated economic savings associated with our sepsis products will be realized directly by hospitals, as the diagnosis and treatment of sepsis patients in the United States in a hospital inpatient setting is currently reimbursed on an inpatient basis under existing diagnosis-related group, or DRG, codes. These codes provide hospitals with a fixed-sum reimbursement for all items and services provided to the patient during a single hospitalization. Therefore, we do not believe we will need to seek new reimbursement codes for our sepsis products.

Another significant unmet clinical need that we believe can be addressed by T2MR is the timely diagnosis and management of impaired hemostasis, which is a potentially life-threatening condition in which a patient is unable to promote the formation of blood clots to stabilize excessive bleeding. For critical trauma patients with impaired hemostasis, diagnostic results are typically required in fewer than 45 minutes to aid clinicians in making the most effective treatment decisions. The need for rapid diagnosis is not met by current diagnostic methods, which typically involve multiple instruments and can take hours to process a patient specimen. As a result, physicians often make critical decisions for treatment of impaired hemostasis with limited or no diagnostic data.

We believe that T2MR can also address the significant unmet need associated with Lyme disease, a tick-borne illness that can cause prolonged neurological disease and musculoskeletal disease. For patients with Lyme disease, early diagnosis and appropriate treatment significantly reduces both the likelihood of developing neurological and musculoskeletal disorders, as well as the significant costs associated with treating these complications. Multiple diagnostic methods are used to test for Lyme disease today, which are labor-intensive, can take weeks to process, and are subject to high false negative rates due to their inability to detect the disease. Because of these limitations, patients are frequently misdiagnosed or are delayed in the diagnosis of this disease.

We believe our combined initial annual addressable market opportunity for sepsis, hemostasis, and Lyme disease is over $3.7 billion in the United States alone, when the market opportunity for T2Candida, T2Bacteria, T2Lyme and our initial hemostasis diagnostic panel is combined. Within the sepsis market in the United States, we estimate that there are approximately 6.75 million critical care and immunocompromised patients who present with symptoms and are at high risk for a bloodstream infection who would be appropriate to be tested by our T2Candida Panel. These patients, along with approximately two million additional patients who receive treatment in the emergency room setting, are also highly susceptible to bacterial infections, for a total of approximately 8.75 million patients who would be appropriate to be tested by our T2Bacteria Panel. Within the hemostasis market, for trauma alone, there are over ten million patients in the United States annually who present with symptoms of impaired hemostasis. These patients often require rapid and frequent hemostasis assessments to determine the presence and severity of abnormal coagulation, or blood clotting. Within the Lyme disease market in the United States, the CDC estimates that the number of patients who present with symptoms is approximately 360,000 and that there are approximately 3.4 million tests run each year in an effort to diagnose Lyme disease, each of whom we believe may be appropriate to be tested with our T2Lyme panel.

Our Strategy

T2MR enables rapid and sensitive direct detection of a range of targets, and we believe it can be used in a variety of diagnostic applications that will improve patient outcomes and reduce healthcare costs. Our objective is to establish T2MR as a standard of care for clinical diagnostics. To achieve this objective, our strategy is to:

- ***Drive Commercial Adoption of Our Sepsis Products by Demonstrating Their Value to Physicians, Laboratory Directors and Hospitals***. We expect our sepsis products to meaningfully improve patient outcomes while reducing costs to hospitals. We have established a targeted, direct sales force in the United States, which is initially focused on educating physicians and demonstrating our clinical and economic value proposition to hospitals that have the highest populations of at-risk critical care and immunocompromised patients. We believe a sustained focus on these hospitals will drive adoption of T2Dx, T2Candida and future T2MR-based diagnostics. As a part of this effort, we will continue to work with thought leaders, conduct clinical and health economic studies and seek publication and presentation of these studies.

- ***Establish a Recurring, Consumables-Based Business Model.*** We are pursuing a consumables-based business model for our products by securing placements of our T2Dx instrument at hospitals and driving utilization of our diagnostic panels starting with T2Candida. We believe this strategy will foster a sustainable and predictable business model with recurring revenue streams.

- ***Broaden Our Addressable Markets in Infectious Disease and Hemostasis.*** Our product development pipeline includes additional instruments and diagnostic panels that provide near-term and complementary market expansion opportunities. Our next sepsis product candidate will focus on bacterial infections, will run on T2Dx and is expected to address the same high-risk patients as T2Candida, while also expanding our reach to a new patient population at increased risk for bacterial sepsis infections. We also are utilizing T2MR to address the challenges of providing rapid hemostasis monitoring, along with rapid and sensitive diagnosis of Lyme disease. We expect to initiate pivotal clinical trials for our bacterial diagnostic panel, T2Bacteria in 2015 and our hemostasis instrument and diagnostic panel, T2Stat and T2HemoStat, in 2016, respectively. We are targeting to commercialize these product candidates after obtaining marketing authorization or regulatory clearance.

- ***Broaden Our Addressable Markets Beyond Infectious Disease and Hemostasis.*** We intend to expand our product offerings by applying T2MR to new applications beyond sepsis, hemostasis and Lyme disease. We plan to conduct internal development and to work with thought leaders, physicians, clinical researchers and business development partners to pursue new applications for T2MR. We believe the benefits of our proprietary technology, including the ability to rapidly and directly detect a broad range of targets, in a wide variety of sample types, will have potential applications within and outside of the *in vitro* diagnostics market, including environmental, food safety, industrial and veterinary applications. For example, we have recently entered into a joint collaboration with Canon U.S. Life Sciences to develop a novel test panel to rapidly detect Lyme disease. The test panel will be developed using our T2MR technology applied for the direct detection of bacteria associated with Lyme disease.

- ***Drive International Expansion.*** We plan to commercialize our current products and product candidates in European and other international markets, and we have initiated a clinical study in Europe for the T2Candida Panel and T2Dx Instrument. We are in the process of developing distribution and commercialization strategies for these markets, and we have recently received CE marking for our T2Candida Panel and T2Dx Instrument.

Our Technology Platform

T2 Magnetic Resonance Platform Overview

We have built an innovative and proprietary technology platform that offers a rapid, sensitive and simple alternative to existing diagnostic methodologies. T2MR is a miniaturized, magnetic resonance-based approach that measures how water molecules react in the presence of magnetic fields. Our proprietary platform is capable of detecting a variety of targets, including:

- molecular targets, such as DNA;
- immunodiagnostics, such as proteins; and

- a broad range of hemostasis measurements.

For molecular and immunodiagnostics targets, T2MR utilizes advances in the field of nanotechnology by deploying particles with magnetic properties that enhance the magnetic resonance signals of specific targets. When particles coated with target-specific binding agents are added to a sample containing the target, the particles bind to and cluster around the target. This clustering changes the microscopic environment of water in that sample, which in turn alters the magnetic resonance signal, or the T2 relaxation signal that we measure, indicating the presence of the target.

For hemostasis measurements, particles are not required because T2MR is highly sensitive to changes in viscosity in a blood sample, such as clot formation, stabilization or dissipation, which changes the T2 relaxation signal. This enables the rapid identification of clinically relevant hemostasis changes.

We also believe T2MR is the first technology that can rapidly and accurately detect the presence of molecular targets within samples without the need for time- and labor-intensive purification or extraction of target molecules from the sample, such as that required by traditional polymerase chain reaction, or PCR, where 90% or more of the target can be lost. We can eliminate these steps because the T2 relaxation signal is not compromised or disrupted by the sample background, even the highly complex sample background that is present after a target amplification process, such as thermocycling. This enables T2MR s low limit of detection, such as 1 CFU/mL, compared to the 100 to 1,000 CFU/mL typically required for PCR-based methods. Over 100 studies published in peer-reviewed journals have featured T2MR in a breadth of applications, including the direct detection and measurement of targets in various sample types, such as whole blood, plasma, serum, saliva, sputum and urine. We believe the potential applications for T2MR extend within and outside of the *in vitro* diagnostics market, including environmental, food safety, industrial and veterinary applications.

Our Instruments

Utilizing T2MR, we have developed and received FDA marketing authorization for the T2Dx, a bench-top instrument for sepsis, Lyme disease, and other applications, and we are developing T2Stat, a compact, fully integrated instrument for hemostasis applications.

T2Dx

T2Dx is an easy-to-use, bench-top instrument that is capable of running a broad range of diagnostic tests and is fully automated from patient sample input to result, eliminating the need for manual work flow steps such as pipetting that can introduce risks of cross-contamination. To perform a diagnostic test, the patient sample tube is snapped onto our disposable test cartridge, which is pre-loaded with all necessary reagents. The cartridge is then inserted into T2Dx, which automatically processes the sample and then delivers a diagnostic test result.

The initial panels designed to run on T2Dx are T2Candida and T2Bacteria, which are focused on identifying life-threatening pathogens associated with sepsis. In 2014 we received FDA marketing authorization for T2Dx and T2Candida, and expect to initiate pivotal clinical trials for T2Bacteria in the second half of 2015. T2Lyme, which is in development, will also run on T2Dx.

T2Stat

We are also applying T2MR to develop T2Stat, which we believe will be the first compact, fully integrated instrument capable of rapidly providing comprehensive hemostasis measurements. T2Stat will run our T2HemoStat panel, which includes a broad set of hemostasis measurements, including platelet function, clotting time and clot degradation, also known as fibrinolysis. We expect to initiate a pivotal clinical trial for T2Stat and T2HemoStat in 2016.

Sepsis

Overview

Sepsis is an illness in which the body has a severe, inflammatory response to a bacterial or fungal infection. It is a life-threatening condition to which individuals with weakened immune systems or chronic illnesses are highly susceptible. Sepsis can lead to shock and organ failure, and is a leading cause of death in the United States with a mortality rate of approximately 30%, almost double the mortality rate of acute myocardial infarction, or heart attack. One out of every two hospital deaths in the United States is attributable to sepsis.

In 2013, the U.S. Department of Health and Human Services reported that sepsis is the most expensive hospital-treated condition in the United States, with an economic burden to hospitals exceeding $20 billion annually, almost double that of acute myocardial infarction. The high cost of treating sepsis is primarily driven by the extended hospitalization of patients. We believe there are many effective, targeted therapeutic choices that could reduce overall hospitalization costs if applied earlier, but clinicians need to more rapidly identify the specific sepsis-causing pathogens in order to make more informed, targeted treatment decisions. Today, the diagnostic standard to identify these pathogens is blood culture-based, despite typically requiring two to five days to generate results.

The following table reflects key statistics from the 2013 U.S. Department of Health and Human Services study regarding the five most expensive hospital-treated conditions:

Rank	Condition	U.S. hospital costs (in billions)	Percentage of total inpatient costs
1	Sepsis	$ 20.3	5.2%
2	Osteoarthritis	14.8	3.8
3	Complication of device, implant or graft	12.9	3.3
4	Liveborn	12.4	3.2
5	Acute myocardial infarction (heart attack)	11.5	3.0

Over 1.6 million individuals are diagnosed with sepsis each year, 1.35 million of whom are at high risk for infection due to their suppressed immune system or their presence in critical care units. Virtually all of these patients are rapidly treated with broad-spectrum antibiotic drugs because there is no diagnostic manner for determining the type of infection. Of these 1.35 million patients with sepsis and at high risk for infection, approximately 40% do not respond to broad-spectrum antibiotic treatment. Of these patients that are non-responsive, approximately 25% of them have a *Candida* infection, with the remaining patients having a bacterial infection. Broad-spectrum antibiotics do not treat these *Candida* and bacterial infections as more targeted drugs are required.

We estimate that approximately 15 million patients are tested for blood stream infections in the United States annually. Of these, approximately 6.75 million are at high risk for a *Candida* infection and an additional two million, or approximately 8.75 million, in total are at high risk for a bacterial infection. We believe that our sepsis products have the potential to enable clinicians to make earlier therapeutic decisions that can reduce the mortality rate for sepsis by over 50% and save the hospitals an estimated $12 billion annually by testing all high risk patients with T2Candida and T2Bacteria.

There is also a significant market opportunity outside the United States for improved sepsis diagnosis, as this disease burdens other countries with similarly high mortality rates and high costs. Each year, over 18 million cases of sepsis are diagnosed worldwide, with estimated mortalities exceeding five million patients, making it a leading cause of death worldwide.

Limitations of Traditional In Vitro Diagnostics for Sepsis

The current standard for identifying bloodstream infections that cause sepsis requires a series of lengthy and labor-intensive analyses that begin with blood culture. Completing a blood culture requires a large volume of a patient s blood, typically 20 mLs or more, which is obtained in two 10 mL draws and placed into two blood culture bottles containing nutrients formulated to grow fungi and bacteria. Before blood culture indicates if a patient is infected, pathogens typically must reach a concentration of 1,000,000 to 100,000,000 CFU/mL. This growth process typically takes two to five days because the pathogen s initial concentration in the blood specimen is often less than 10 CFU/mL. A negative test result always requires a minimum of five days. A positive blood culture typically means that some pathogen is present, but additional steps must be performed to identify the specific pathogen in order to provide targeted therapy. These additional steps, which typically must be performed by a highly trained technician, may involve any of (i) a staining procedure for inspection on a microscope slide, (ii) PCR amplification and (iii) mass spectrometry. These steps require a preceding positive blood culture specimen because they need a high concentration of cells generated by the blood culture process for analysis.

For PCR-based diagnostics, there is a requirement for extraction of target cells from the sample into a clear solution, where 90% or more of the cells can be lost. Extraction into a clear solution is needed because existing diagnostic detection methods cannot detect the targeted pathogen due to the complex background of the sample itself. While PCR amplifies the target signal, this loss of target cells impairs the ability to detect, resulting in typical limits of detection of 100 to 1,000 CFU/mL, which is insufficient for species-specific sepsis diagnostics.

Blood culture-based diagnostics have substantial limitations, including:

- **Time to Result Delays Targeted Treatment.** Blood culture-based diagnostics typically require a minimum of two and as many as five or more days to identify a pathogen species, and blood culture always requires at least five days to generate a negative test result.

- **Antimicrobial Therapy Can Cause False Negative Results.** Antimicrobial therapies may be administered to a patient prior to taking a blood sample. As a result, the therapeutic agent is contained in the blood sample and its ability to stop or slow the growth of pathogens can delay or completely inhibit the growth of the pathogen during the blood culture process leading to time delays in detection or false negative results.

- **Slow-Growing Pathogens Can Cause False Negative Results.** Some sepsis pathogens grow slowly or not at all and can require up to five or more days to reach sufficient concentrations to be detected by blood culture-based diagnostics. Blood culture procedures are typically stopped after five days and declared negative. Often, pathogens that grow too slowly are not detected by blood culture during this time frame, leading to a false negative diagnosis. For example, *C. glabrata*, one of the most lethal species of *Candida* due to its growing resistance to antifungal therapy, often requires more than five days of growth to reach a detectable concentration, and therefore is frequently undetected by blood culture.

- **Labor-Intensive Workflow Increases Costs and May Delay Targeted Treatment.** Blood culture is only the first step in identifying a pathogen that causes sepsis. After a blood culture is determined to be positive, highly trained technicians are required to perform multiple post-culture procedures on the blood culture specimen to identify the specific pathogen. These additional procedures can be expensive and time-consuming and may delay targeted treatment.

Given the typical two- to five-day time to result for blood culture-based diagnostics, the first therapy for a patient at risk of sepsis is often broad-spectrum antibiotics, which treat some but not all bacteria types and do not address fungal infections. Some physicians may use first-line, antifungal therapy for patients at very high risk for fungal infection, or use antifungal therapy if the patient is not responding to broad-spectrum antibiotics while they are still awaiting the blood culture-based result. This therapeutic approach may still not treat the growing number of patients infected with the antimicrobial-resistant species nor may it be the best choice, as the type of therapy is dependent on the specific pathogen causing the infection, which is unknown.

This inefficient therapeutic approach has resulted in unnecessary treatment of a significant number of high-risk patients with expensive and often toxic therapies that can worsen a patient s condition. Such treatments may extend for many days while clinicians await blood culture-based diagnostic results. The overuse of ineffective, or even unnecessary, antimicrobial therapy is also the driving force behind the spread of antimicrobial-resistant pathogens, which the U.S. Centers for Disease Control and Prevention, or the CDC, recently called one of our most serious health threats. The CDC has

specifically noted increasing incidence of *Candida* infections due to azole- and echinocandin-resistant strains and considers it a serious threat level. According to the CDC, at least two million people in the United States acquire serious infections each year that are resistant to one or more of the antimicrobial therapies used to treat these patients. At least 23,000 of these people are estimated to die as a direct result of the resistant infections and many more may die from other conditions that are complicated by a resistant infection. Further, antimicrobial-resistant infections add considerable and avoidable costs to the already overburdened U.S. healthcare system, with the total economic cost estimated to be as high as $20 billion in excess of direct healthcare costs, with additional costs to society as high as $35 billion, due to lost productivity.

Our Solution

T2MR delivers what we believe no other technology currently available can: a rapid, sensitive and simple diagnostic platform that enables sepsis applications, including T2Candida and T2Bacteria, that can identify specific sepsis pathogens directly from an unpurified blood sample in hours instead of days at a level of accuracy equal to or better than blood culture-based diagnostics. We believe T2MR sepsis applications provide a pathway for more rapid and targeted treatment of infections, potentially reducing the mortality rate by as much as 75% if a patient is treated within 12 hours of suspicion of infection and significantly reducing the cost burden of sepsis. Each year, approximately 500,000 patients in the United States die from sepsis. According to a study published by *Critical Care Medicine* in 2006, in sepsis patients with documented hypotension, administration of effective antimicrobial therapy within the first hour of detection was associated with a survival rate of 79.9% and, over the ensuing six hours, each hour of delay in initiation of treatment was associated with an average decrease in survival of 7.6%; the survival rate for septic patients who remained untreated for greater than 36 hours was approximately 5%.

We believe T2MR sepsis applications address a significant unmet need in *in vitro* diagnostics by providing:

- **Limits of Detection as Low as 1 CFU/mL.** T2MR is the only technology currently available that can enable identification of sepsis pathogens directly from a patient s blood sample at limits of detection as low as 1 CFU/mL.

- **Rapid and Specific Results As Fast As Three Hours.** T2MR is the only technology that can enable species-specific results for pathogens associated with sepsis, directly from a patient s blood sample, without the need for blood culture, to deliver actionable results as fast as three hours.

- **Accurate Results Even in the Presence of Antimicrobial Therapy.** T2MR is the only technology that can reliably detect pathogens associated with sepsis, including slow-growing pathogens, such as *C. glabrata*, directly from a patient s blood sample, even in the presence of an antimicrobial therapy.

- **Easy-to-Use Platform.** T2MR eliminates the need for sample purification or extraction of target pathogens, enabling sample-to-result instruments that can be operated on-site by hospital staff, without the need for highly skilled technicians.

Our first FDA authorized products, T2Dx and T2Candida, focus on the most lethal form of common blood stream infections that cause sepsis, *Candida*, which has an average mortality rate of approximately 40%, and according to a 2005 report published in *Antimicrobial Agents and Chemotherapy*, this high mortality rate can be reduced to 11% with the initiation of targeted therapy within 12 hours of presentation of

symptoms. Currently, a typical patient with a *Candida* infection averages 40 days in the hospital, including nine days in intensive care, resulting in an average cost per hospital stay of over $130,000 per patient. In a study published in the *American Journal of Respiratory and Critical Care Medicine* in 2009, providing targeted antifungal therapy within 24 hours of the presentation of symptoms decreased the length of hospital stay by approximately ten days and decreased the average cost of care by approximately $30,000 per patient. In addition, many hospitals initiate antifungal drugs, such as Caspofungin or Micafungin, while waiting for blood culture-based diagnostic results. We estimate this practice costs approximately $500 per patient and is currently in use for over 40% of high-risk patients on average and for all high-risk patients in some hospitals. A negative result from T2Candida can provide timely data allowing physicians to avoid unnecessary antifungal treatment and potentially reduce the treatment cost further.

We believe that by identifying the specific species of *Candida*, physicians can administer the most effective therapy, which will significantly improve patient outcomes and reduce hospital costs. We further believe that the adoption of T2Dx and T2Candida can decrease both the high mortality rate and excessive costs of *Candida* infections because these products can enable clinicians to make earlier and more informed decisions by providing positive test results to direct therapy and negative test results to reduce the use of antifungal drugs.

We surveyed 111 decision-makers involved with laboratory purchasing, including laboratory directors, hospital administrators and infectious disease physicians, in a web-based survey to seek their views on acceptable pricing for T2Candida in exchange for an honorarium. Based on the survey, we believe that with 90% sensitivity, 95% specificity and a cost savings of $650 per tested patient, T2Candida would be adopted by nearly 50% of physicians at a selling price of $200 per test. However, we expect that cost savings will be $800 per patient and we observed overall sensitivity of 91.1% and specificity of 99.4% in our direcT2 clinical trial described below. Additionally, in this survey, 95% of laboratory directors and hospital administrators, along with 89% of infectious disease physicians, either strongly agreed or agreed that initiating appropriate antifungal therapy within 12 hours of the patient presenting with symptoms would be likely to provide the following benefits:

- reduction in the mortality rate from an average of 40% to approximately 10% for candidemia patients;

- direct cost-savings as a result of an average of nine fewer days of hospitalization for each candidemia patient, including two fewer days of stay in the intensive care unit; and

- a meaningful decrease in antifungal therapy utilization in a hospital due to cessation of therapy based on a negative test result.

The surveyed physicians also indicated that, on average, they would order T2Candida for approximately 75% of their patients considered at-risk for *Candida* infections. In the United States, we are focusing our sales efforts on the 450 hospitals that have the highest concentration of patients at risk for *Candida* infections. In each of these institutions, over 5,000 patients present with symptoms of candidemia annually. We believe that with appropriate sales efforts and medical education, all of these patients will eventually be tested, representing a total recurring revenue opportunity of $1 million in each of our target accounts.

We are also developing T2Bacteria, a multiplex diagnostic panel that detects the major bacterial pathogens associated with sepsis that are frequently not covered by first-line antibiotics. T2Bacteria will also run on T2Dx and is expected to address the same approximately 6.75 million symptomatic high-risk patients as T2Candida while also expanding our reach to a new population of patients who are at increased risk for bacterial infections, including an additional two million people presenting with symptoms of infection in the emergency room setting. We expect that T2Bacteria will achieve similar performance capabilities and provide similar benefits as T2Candida.

Clinical Utility

direcT2 Clinical Trial Clinical Infectious Disease

In 2013 and 2014, we conducted a pivotal clinical trial for our T2Dx Instrument and our T2Candida Panel, or the direcT2 trial. Our direcT2 trial consisted of two patient arms. The first arm, known as the Prospective Arm, consisted of 1,501 samples from patients with a possible infection. The second arm, known as the Contrived Arm, consisted of 300 samples, of which 250 patient specimens were labeled contrived because each contained a known quantity of *Candida* CFUs that were manually added to each sample, or spiked, at clinically relevant concentrations, while the remaining 50 patient specimens were specifically known not to contain *Candida*. The direcT2 trial was designed to evaluate the sensitivity and specificity of T2Candida on the T2Dx instrument.

Sensitivity is the percent concordance, or the percentage of sample results that agree with a reference, or comparative, method for positive results. Specificity is the percent concordance to a reference method for negative results. If a sample does not agree with the result of a referenced method, it is considered discordant. In our clinical trial, the Prospective Arm was compared to blood culture and the Contrived Arm was compared to the known state, which means that it was in the known presence or absence of added *Candida* organisms.

The design of the direcT2 trial was reviewed by the FDA as part of pre-submission communications. The purpose of the direcT2 trial was to determine the clinical performance of T2Candida running on the T2Dx by identifying the following:

- clinical specificity of T2Candida results as compared to *Candida* negative blood culture results in specimens collected from patients in the Prospective Arm;

- clinical specificity of T2Candida results as compared to *Candida* negative samples collected from patients in the Contrived Arm;

- clinical sensitivity of T2Candida results as compared to the known *Candida*-positive specimens collected from patients in the Contrived Arm; and

- clinical sensitivity calculations of T2Candida results compared to the *Candida*-positive blood culture results in specimens collected from patients in the Prospective Arm.

50 known negative samples and 250 contrived samples (50 samples for each of the five *Candida* species included in the T2Candida Panel) were prepared and run in a blinded manner at the same clinical sites used for processing the prospective samples. The positive contrived samples were prepared by spiking clinical isolates into individual patient specimens at concentrations determined through publications and discussions with the FDA to be equivalent to the clinical state of patients who presented with symptoms of a *Candida* infection. 20% of the positive contrived samples were spiked at concentrations levels of less than 1 CFU/mL. The contrived samples were collected from patients referred for a diagnostic blood culture per routine standard of care the same population of patients from whom prospective samples were collected. Unique isolates of the species were used for each patient sample, which means a total of 50 unique isolates were tested for each of the five species of *Candida* for a total of 250 unique isolates.

In addition to the pivotal clinical trial data that we submitted to the FDA, we also provided data from an analytical verification study to determine the limit of detection, or LoD, for each species identified by our T2Candida Panel. The LoD was defined as the lowest concentration of *Candida* that can be detected in 95% of at least 20 samples tested at a single concentration.

The T2Candida Panel reports three results, where species are grouped together according to their responsiveness to therapy. *Candida albicans* and/or *Candida tropicalis* are reported as a single result, *Candida parapsilosis* is a single result, and *Candida krusei* and/or *Candida glabrata* are reported as a single result. Specificity and sensitivity are calculated for each reported result.

There are five relevant species of *Candida*, each of which were analyzed in the direcT2 trial. Each are listed in abbreviated form in the tables below. These species are *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and *Candida glabrata*. The typical naming convention for a species is to abbreviate by using the first letter of the first word and the full second word; for example, *Candida krusei* is abbreviated as *C. krusei*. In the tables below, we also abbreviate each species name by the first letter of the second word; for example, *Candida albicans* and *Candida tropicalis* is A/T.

The following tables illustrate the results of the direcT2 trial. The primary sensitivity and specificity analysis is presented in Table A, followed by sub-analyses in Tables B and C. Additional data on the LoD and the time to results of T2Candida and T2Dx are included in the remaining tables.

Table A

T2Candida Performance Characteristics

	Overall Sensitivity	Overall Specificity
Number of Tests (%)	234/257 (91.1%)	5114/5146 (99.4%)

Table B

Overall Sensitivity and Specificity by Test

		95% Confidence Interval
Specificity:		
A/T (*C. albicans/C. tropicalis*)	1679/1697 (98.9%)	98.3-99.4%
P (*C. parapsilosis)*	1736/1749 (99.3%)	98.7-99.6%
K/G (*C. krusei/C. glabrata)*	1699/1700 (99.9%)	99.7-100.0%
Total:	5114/5146 (99.4%)	99.1-99.6%
Sensitivity:		
A/T (*C. albicans/C. tropicalis)*	96/104 (92.3%)	85.4-96.6%
P (*C. parapsilosis)*	49/52 (94.2%)	84.1-98.8%
K/G (*C. krusei/C. glabrata)*	89/101 (88.1%)	80.2-93.7%
Total:	234/257 (91.1%)	86.9-94.2%

Table C

Study Arm Sensitivity and Specificity by Test

		95% Confidence Interval
Specificity (Prospective tests):		
A/T (*C. albicans/C. tropicalis*)	1479/1497 (98.8%)	98.1-99.3%
P (*C. parapsilosis)*	1487/1499 (99.2%)	98.6-99.6%
K/G (*C. krusei/C. glabrata)*	1499/1500 (99.9%)	99.6-100.0%
Total:	4465/4496 (99.3%)	99.0-99.5%
Sensitivity (Prospective tests):		
A/T (*C. albicans/C. tropicalis)*	2/4 (50.0%)	6.8-93.2%
P (*C. parapsilosis)*	2/2 (100.0%)	15.8-100.0%
K/G (*C. krusei/C. glabrata)*	1/1 (100.0%)	2.5-100.0%
Total:	5/7 (71.4%)	29.0-96.3%
Specificity (Contrived tests):		
A/T (*C. albicans/C. tropicalis)*	200/200 (100.0%)	98.2-100.0%
P (*C. parapsilosis)*	249/250 (99.6%)	97.8-100.0%
K/G (*C. krusei/C. glabrata)*	200/200 (100.0%)	98.2-100.0%
Total:	649/650 (99.8%)	99.1-100.0%
Sensitivity (Contrived tests):		
A/T (*C. albicans/C. tropicalis)*	94/100 (94.0%)	87.4-97.8%
P (*C. parapsilosis)*	47/50 (94.0%)	83.5-98.7%
K/G (*C. krusei/C. glabrata)*	88/100 (88.0%)	80.0-93.6%
Total:	229/250 (91.6%)	87.4-94.7%

Table D

T2Candida Limit of Detection

Species	Final LoD CFU/mL
C. albicans	2
C tropicalis	1
C. parapsilosis	3
C. glabrata	2
C. krusei	1

Table E

Sensitivity Sub-Analysis: Sensitivity by Species Relative to LoD

		≥ LoD		< LoD	
	LoD (CFU/ml)	Sensitivity	95% Confidence Interval	Sensitivity	95% Confidence Interval
C. albicans	2	39/39 (100.0%)	91.0-100.0%	9/11 (81.8%)	48.2-97.7%
C. glabrata	2	35/37 (94.6%)	81.8-99.3%	7/13 (53.8%)	25.1-80.8%
C. krusei	1	40/40 (100.0%)	91.2-100.0%	6/10 (60.0%)	26.2-87.8%

C. parapsilosis	3	32/32 (100.0%)	89.1-100.0%	15/18 (83.3%)	58.6-96.4%
C. tropicalis	1	38/40 (95.0%)	83.1-99.4%	8/10 (80.0%)	44.4-97.5%
Total:					