CARB-X Stewardship & Access Plan
T2 Biosystems
Project title: T2MR for direct whole blood pathogen and resistance identification
Product: The T2Resistance Panel

Product Definition

The T2Resistance® Panel is a direct-from-blood diagnostic designed to detect genetic markers associated with antibiotic-resistant gram-negative and gram-positive bacterial bloodstream infections. The T2 Resistance Panel detects the following antimicrobial resistance genes which indicate implied resistance or presence of a resistance enzyme:

- *mecA / mecC* → Methicillin-resistant Staphylococcus spp.
- *vanA / vanB* → Vancomycin-resistant Enterococci (VRE)
- KPC → Carbapenemase
- AmpC CMY / DHA → AmpC β-Lactamase
- OXA-48 Group → Carbapenemase
- NDM / VIM / IMP → Carbapenemase (MBL)
- CTX-M 14/15 → Extended spectrum β-lactamases (ESBL)

The T2Resistance Panel utilizes the same T2Dx® Instrument as the T2Bacteria® and T2Candida® Panels – which are FDA-cleared and CE-marked panels for detection of sepsis-causing bloodstream infections direct from a patient's blood sample, without requiring blood culture results. The T2Dx Instrument is an integrated, sample-to-answer diagnostic system that does not require additional sample preparation.

The T2Resistance Panel would be used similarly across different countries and regions since the T2Resistance Panel identifies the most serious resistance genes on the antibiotic-resistance threat list published by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). The T2Resistance Panel and T2Dx Instrument are designed for moderate-complexity in-hospital settings primarily serving patients in intensive care units and the emergency department.

The intended use of the CE-IVD marked T2Resistance Panel:
Note that the intended use of the T2Resistance Panel may be different for a FDA-cleared product in the future.

The T2Resistance Panel run on the T2Dx Instrument is a qualitative T2 Magnetic Resonance (T2MR®) test for the direct detection of molecular markers of antimicrobial resistance in EDTA human whole blood specimens from patients with suspected bacteremia. The T2Resistance Panel detects thirteen molecular markers of resistance and categorizes them into the following seven groups:

1. *bla*KPC
2. *bla*CTX-M
3. *bla*NDM / *bla*VIM / *bla*IMP

4. *bla*OXA-48 Group
5. *vanA* / *vanB*
6. *mecA* / *mecC*
7. AmpC (*bla*CMY / *bla*DHA)

The T2Resistance Panel does not distinguish individual molecular markers of antimicrobial resistance within a given group.

The T2Resistance Panel detects molecular markers that are associated with organisms that are recognized to cause blood stream infections. Detection of the molecular marker may be indicative of potential infection with an antibiotic resistant organism.

Negative results for these select molecular markers of antimicrobial resistance do not indicate susceptibility, as multiple mechanisms of resistance exist, nor do they indicate absence of an infectious pathogen.

The T2Resistance Panel is an aid for the early indication of the presence of molecular markers of resistance that may be due to an antibiotic resistant organism and results should be used in conjunction with other clinical and laboratory data. Concomitant blood cultures are necessary to recover organisms for further identification, including susceptibility testing or epidemiological typing.

Identify Obstacles and Constraints to Stewardship and Access

Use of the T2Dx Instrument® and T2Resistance Panel requires stable power, controlled temperature (air conditioning), and cold chain. Facilities do exist in low- and middle-income countries where the instrument and product could be deployed, however access to these requirements is not as prevalent in low resource settings. While there are environmental and operational challenges previously mentioned, the operation of the instrument and assay is simple to use with appropriate application training and adherence. Clinical interpretation does require appropriate training and clinical staff.

The T2 family of products have been specifically designed to enable effective antimicrobial stewardship. With the identification of blood stream infection causing pathogen within 3-5 hours after blood sample draw, the clinician is able to better achieve the right antibiotic therapy, at the right time (within hours), for the right patient. Furthermore, our products enable rapid identification of the genes and species associated with antibiotic resistance enabling appropriate therapy and the reduction of unnecessary antibiotic use. Most importantly, these tests can enable more patients to get on the right targeted therapy faster, potentially reducing mortality, hospitalization cost, development of resistance, and empiric use of antibiotics. The results can also be used to enable antimicrobial resistance surveillance, local antibiograms, and design of empiric therapy guidelines.

The lack of adequately trained clinicians who understand the value of rapid molecular diagnostics and departmental silos may make the product less actionable. Additionally lack of communication between departments may prohibit the development of multi-disciplinary antimicrobial stewardship programs that understand the importance of rapid diagnosis of resistant pathogens. Lastly, lack of availability of certain antibiotics could potentially affect use of the T2Resistance Panel. An example would be lack of availability of carbapenems might make the information provided by the product (i.e. identification of CTX-M 14/15 → Extended spectrum β-lactamases (ESBL)) less actionable.

Strategies to Ensure Marketing Approvals are Received in a Timely Manner in the Targeted Territories

The T2Resistance Panel was granted a CE mark in November of 2019 meeting the requirements of the In-Vitro Diagnostics Directive (98/79/EC, IVDD) and allowing marketing of the T2Resistance Panel within the European Economic Area (EEA). Compliance with In Vitro Diagnostic Medical Devices Regulation (**EU**) 2017/746 (**IVDR**) is planned. In 2019, the FDA granted "Breakthrough Device" designation for the T2Resistance Panel, reflecting the purpose of the panel to rapidly identify resistant infections. The T2Resistance Panel has not yet been submitted to the FDA for premarket review and is not currently available for clinical use in the United States. Enrollment in a US clinical trial to support FDA submission has been completed and a future submission is planned.

After FDA clearance of the T2Resistance Panel we anticipate supporting additional studies demonstrating the clinical utility of the product, just as we have done following the FDA clearance/CE marking of the T2Bacteria and T2Candida Panels. We do not currently have plans for additional clinical trials to expand indications following FDA clearance.

We welcome the CDC's newly released sepsis guidelines for hospitals. Official clinical definitions of sepsis have been updated - the most recent is "Sepsis-3," published in February 2016 - but there are still significant opportunities for improvement. Guidelines for identifying and treating sepsis patients in the hospital are essential, but there is a need for recommendations and guidelines to be updated with new diagnostic technologies that may be beneficial in identifying sepsis, the risk for sepsis and reducing the time needed to discontinue, narrow, or broaden antibiotic therapy as appropriate.

We currently distribute products in many countries including the following: United States of America (including Puerto Rico, and the U.S. Virgin Islands), Australia, Austria, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kuwait, Latvia, Lithuania, Macedonia, New Zealand, Mexico, Norway, Portugal, Romania, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Republic of Korea, Sweden, Switzerland, Taiwan, United Arab Emirates, and United Kingdom. Of these countries, the following countries would be considered LMIC: Bosnia-Herzegovina, Egypt, Macedonia, Mexico, Serbia and South Africa.

Strategies to Support Stewardship and Access in the Other Territories

Our focus is on the need to complete U.S. FDA regulatory approval of the T2Resistance Panel. We will continue to explore opportunities to bring T2Resistance and other T2 sepsis products into new markets, including LMIC.

Strategies for Exploiting Project IP Rights in the Other Territories

We do not currently foresee that there will be opportunities to out-source licensing or manufacturing.

Strategies for Monitoring Effectiveness of Stewardship and Access Activities

We do not currently have plans to report annually stewardship and access plans publicly beyond our obligations to CARB-X.