Landscape of benchtop immunoassay platforms for near patient testing: The MAPDx Program

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ABBREVIATIONS

AMR – Antimicrobial resistance
CE-IVD – Conformité Européenne (European conformity) with the European Union *In Vitro* Device directive
CDC – Centers for Disease Control and Prevention
CMV – Cytomegalovirus
CRP – C-reactive protein
DNA – Deoxyribonucleic acid
EC – European Commission
FDA – Food & Drug Administration
FIND –Foundation for Innovative New Diagnostics
HRS – High resource settings
LAMP – Loop-mediated isothermal amplification
LMICs – Low- and middle-income countries
MAPDx – Multiplex multi-analyte platform diagnostic
MAPDxP – MAPDx Program
MSF – Médecins Sans Frontières
NPT – Near patient testing
PRD – Product Requirements Document
POC – Point of care
R&D – Research and development
RLS – Resource limited settings
RNA – Ribonucleic acid
SFWS – severe febrile illness without a known source
TBD – To be determined
TPP – Target product profile
USB – Universal Serial Bus
VRE – vancomycin-resistant enterococci
WHO – World Health Organization

1. EXECUTIVE SUMMARY

Introduction

The Febrile Illness Diagnostic Program, hosted by Médecins Sans Frontières (MSF) USA, has been examining the feasibility of developing a novel diagnostic capable of simultaneous testing for multiple pathogens and different analyte types (MAPDx) to improve MSF's ability to diagnose and manage patients presenting with severe febrile illness without a known source. MSF partnered with FIND and the World Health Organization (WHO) to develop a target product profile (TPP) for MAPDx to define minimal and optimal end-user requirements. A main feature of MAPDx is its ability to detect both nucleic acids and immunoassay targets in the same platform from the same sample. To identify platforms of interest and relevance to the MAPDx program, FIND conducted a landscape of immunoassay platforms that are either commercially available or in development and assessed them for their relevance to the MAPDx TPP.

Through a comprehensive technology search conducted from Q3 2017 through Q1 2018, 54 immunoassay platforms were identified, and key technology features were compared to the MAPDx TPP (Appendix 1). The nine platforms most closely matching the TPP are listed in alphabetical order by manufacturer below.

Table 1: Summary of top technologies of relevance to the MAPDx program

Manufacturer	Platform
Abionic	abioSCOPE
Baebies	Finder
biosurfit	Spinit
BLINK Dx	BLINK ONE
BluSense Diagnostics	BluBox
MBio Diagnostics, Inc.	LightDeck Technology
Randox	Evidence MultiSTAT
Singulex	"POC Platform"
SpinDiag	LabDisk

Conclusions

- ***No currently available platform meets the MAPDx TPP minimal characteristics.*** The main characteristics that were not met include power requirements, environmental stability, throughput (random access, multiple ports), and in most cases, capability to detect multiple analyte types (e.g. nucleic acids and immunoassay targets in the same platform)
- Technologies do exist that demonstrate the technological feasibility of the MAPDx vision
- Technologies will require significant investment to achieve the MAPDx minimal TPP characteristics and further resources to achieve the optimal specifications
  - The extent of the product development effort depends on the level of core technology maturity (early stage vs. commercial product available)
- We have identified nine immunoassay platforms with key attributes of relevance to the MAPDx program (Table 31). Further details and assessment insights are provided in this report for each platform listed in the table.

2. PURPOSE AND SCOPE

2.1 Background

Clinicians and patients in low- and middle-income countries (LMICs) frequently lack access to reliable laboratory services, particularly outside of large population centers. When laboratory services are available, a limited test menu hinders clinical decision-making and antimicrobial stewardship, leading to empiric treatment and suboptimal patient outcomes. To revolutionize laboratory capabilities in LMIC settings, Médecins Sans Frontières (MSF) has partnered with FIND and the World Health Organization (WHO) to develop a target product profile (TPP) describing a new diagnostic platform for near-patient testing of multiple pathogens and different analytes types (MAPDx). The MAPDx platform would offer several advantages including: testing for multiple pathogens in a panel from the same sample rather than sequential testing of multiple samples; testing for multiple-analyte types to detect a pathogen along the kinetics of infection or pathogens that require different detection technologies; and a semi-open design allowing for a wide menu of assay panels. The combination of these features would result in fewer diagnostic platforms that need to be maintained and a fast, clinically useful result from a single specimen.

Because fever is one of the most common reasons for admission to hospitals in resource-limited settings (RLS), the initial assay panel for MAPDx targets severe febrile illness without a known source (SFWS). Many fever causing pathogens present with similar symptomology, thus individuals with SFWS are severely ill but lack a clear diagnosis, making effective patient management a challenge for clinicians. Therefore, the initial test panel for SFWS is intended for uses in general patient populations for testing with a single blood specimen for individual patient management. The Febrile Illness Diagnostic Program, hosted by MSF USA, has continued to examine the feasibility of developing the envisioned MAPDx, which would require a platform capable of detecting multiple analyte types (nucleic acids and immunoassay targets).

2.2 Project aim

The purpose of this report to is to identify immunoassay platforms (either immunoassay only or platforms capable of immunoassay and detection of other analyte classes/types) of relevance to the MAPDx program (MAPDxP) using the recently published MAPDx target product profile as a reference (see Appendix 1). The figure below provides an overview of how the molecular and immunoassay landscape outputs will inform the top list of platforms relevant to the MAPDxP.

Important Note: The objective of this landscape of immunodiagnostic technologies is to address the requirements of the MAPDx TPP: it is focused on the requirements of the MSF project. ***This is not a general landscape of immunodiagnostic platforms. Furthermore, the technology review was completed in February 2018 and is only current to that date in time.***

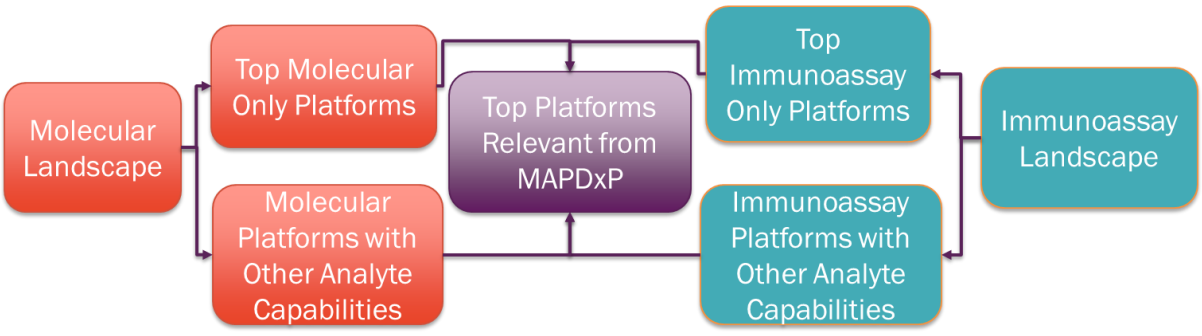

Figure 1: Overview of diagnostic landscapes to inform the MAPDx program

3. METHODOLOGY

A search for potential immunoassay platforms of interest was conducted from Q3 2017 through Q1 2018 using multiple sources, including the following:

1. Literature searches for immunoassay platforms appropriate for RLS (search terms – “new, novel, comparison, and evaluation” used in combination with “immunoassay diagnostic, multiplex immunoassay diagnostic, and “platform instrument”)
2. Internet searches to identify multiplex immunoassay platforms and companies
3. Attendance in-person at three scientific meetings: Southern California American Society for Microbiology (SCASM; Fall 2017), Association of Molecular Pathology (AMP) Salt Lake City, UT, USA Fall 2017), and the American Association for Clinical Chemistry (AACC, Sand Diego, CA, USA, 2017 via Sabine Dittrich (FIND))
4. Diagnostic industry conference agenda: JP Morgan, BioInvestor Forum, Molecular Medicine Tri-Conference, CHI Molecular Diagnostics Europe, Next Generation Dx Summit, Biomedical Advanced Research & Development Authority (BARDA) Industry Day 2016, BIO-Europe 2017, and SELECTBIO 2017 (multiple conferences).
5. Agendas, abstracts, available online presentations from scientific meetings/conferences (American Society for Microbiology (ASM) “Microbe” meeting, European Congress of Clinical Microbiology and Infectious Disease, Infectious Disease Society of America ID Week, and American Association for Clinical Chemistry)
6. Diagnostic industry online reports, news, and press releases (e.g., Genomeweb and Fierce Biotech)
7. Phone interviews with representatives from Baebies and SpinDiag
8. Reviewed FIND technology database on immunoassay diagnostic companies
9. Vetted list with FIND staff with expertise in immunoassay diagnostics

This comprehensive search identified 54 potential technologies. To identify key technologies of interest to the MAPDx program, technologies were evaluated based on the published FIND template for technology partner selection guidelines. A full description of the FIND standard criteria can be found at: https://www.finddx.org/wp-content/uploads/2018/01/Tech-Partner-Selection-Guidelines_QP-02-08-02_V3.0.pdf. Technologies were also compared to the MAPDx TPP, and the top nine technologies were selected based on key features which satisfied the TPP requirements or could be adapted to do so. Each of the following summaries of those nine technologies has been reviewed by the company. The technologies are listed below in alphabetical order by manufacturer.

4. TOP IMMUNOASSAY PLATFORMS OF RELEVANCE TO THE MAPDX PROGRAM

a. Platform: abioSCOPE® / Manufacturer: Abionic

Location	Lausanne, Switzerland
Website	https://abionic.com/en/
Time to Market	On Market

Technology Overview
Nanofluidic immunoassay; fluorescent molecular complexes are formed on a nanosensor which are then measured optically by an integrated fluorescent microscope laser. Three versions of instrument for pharmacy, hospital/ICU and clinician's office.

Assay Specifications	
Turnaround Time	< 5 minutes
Sample Processing	No sample processing required
Sample Types	Whole blood
Sample Volume	0.05 mL
Multiplexing	10 targets
Assay Types	Immunoassays

Source: https://abionic.com/en/

Company background:

Abionic is an early stage, privately held diagnostic company located in Lausanne, Switzerland. It was founded in 2010 as a spin-off from the Swiss Federal Institute of Technology (EPFL), also in Lausanne. Abionic has focused their efforts in POC, allowing “access to lab quality blood analysis where there is no or insufficient infrastructure in place.” They have three versions of the abioSCOPE instrument for the pharmacy, hospital/ICU and clinician office markets. The instruments have the same technology, but different displays, external appearance, and assay availability. They currently have CE-IVD assays for allergy (10 multiplex, semi-quantitative for primary care and quantitative for Allergy Experts), sepsis risk biomarker (pancreatic stone protein) and iron deficiency (ferritin). CRP and D-dimer and other undisclosed assays are in development. The allergy test was FDA registered in 2017, and the company is currently seeking distribution partners to commercialize their products worldwide. They anticipate FDA clearance of the sepsis risk assay in 2019.

Technology overview:

The abioSCOPE uses fluorescent nanofluidic immunoassay technology. Biosensors with chemically linked antigens interact with analytes from a patient sample. These form immobilized fluorescent-labeled molecular complexes that are detected and quantified optically using an integrated laser without any washing steps. Because of the nanofluidic configuration, biomolecular interactions are accelerated, and the test result is available in 5 minutes from sample to answer after the specimen is combined with a reagent solution. There is no sample preparation step or pre-incubation step. All types of immunoassay formats can be performed. The assays take place in a disposable “capsule/cartridge” which is placed into a disc-shaped mounting plate, which is then inserted into the instrument similar to a DVD being inserted into a DVD player. The system can handle whole blood (capillary or venous) and serum/plasma samples. A typical specimen is a 50 µL “fingerstick” sample.

b. Platform: FINDER / Manufacturer: Baebies

Location	Durham, NC
Website	https://www.baebies.com
Time to Market	End of 2019 (Hyperbilirubinemia)

Technology Overview
The FINDER platform uses digital microfluidics for rapid manipulation of separate droplets by electrical control of surface tension (electrowetting) to perform bioassay protocols. FIDNER is capable of on-board plasma separation, dilution, reagent mixing and rapid detection for panels of disease or condition specific tests. Enzymatic assays are detected via absorbance or fluorescence. Immunoassays use magnetic beads coupled to antibodies.

Assay Specifications	
Turnaround Time	< 15 minutes
Sample Processing	Fully integrated on-cartridge
Sample Types	Whole blood
Sample Volume	0.05 mL
Multiplexing	Up to 7 targets
Assay Types	Biochemical, enzymatic & immunoassays

Source: www.baebies.com

Company background:

Baebies is an early stage, privately held diagnostic company in Durham, North Carolina, USA that is focused on “better tools for global newborn and pediatric testing.” The founders of Baebies developed the “digital microfluidics” technology at Advanced Liquid Logic, which was acquired by Illumina in 2013. Baebies was founded in 2014 and licensed this core technology. The company currently manufactures and markets a high throughput centralized laboratory newborn screening platform (“SEEKER®”) with CE-IVD and FDA (*de novo*) authorized assays for lysosomal storage diseases. Their FINDER technology is currently in late stages of development and will be their second platform designed for various near patient settings, including hospital nurseries, neonatal intensive care units, birthing centers and physician offices. Although currently focused on the US and European markets, Baebies eventually aspires to have a worldwide impact: “the ‘e’ in Baebies is for everyone, as in everyone deserves a healthy start,” according to the company. In an Xconomy article, the company stated, “In addition to screening for rare diseases in newborns in the Western world, Baebies sees its technology offering screening, diagnosis and monitoring capabilities globally in emerging markets that do not yet have laboratory testing infrastructure.” The initial planned menu for FINDER includes a multiplex test for total serum bilirubin, albumin, and glucose-6-phosphate dehydrogenase (G6PD). The company has several NIH SBIR grants to develop panels of tests on the FINDER platform for jaundice, hypoglycemia, acute kidney injury, thyroid function, heparin / coagulation monitoring, and rapid NAT for congenital CMV infection.

Technology overview:

Baebies’ technology for FINDER is based on digital microfluidics in a disposable cartridge format with preloaded liquid and dried reagents. Digital microfluidics enables rapid, automated manipulation of separate fluid droplets by electrical control of surface tension (electro-wetting) in a network of connected electrodes that move the liquids (sample and reagents) to perform tests. Currently, multiple tests (up to seven targets) are possible at the same time in one cartridge. Multiple independent assays and classes of assays (e.g.,

biochemical, enzymatic and immunoassays) can be run on the same cartridge at the same time for quantitative results. The instrument has a small footprint (eight inches wide). Baebies has demonstrated assays using whole blood, plasma, serum, dried blood spot, saliva, and urine samples with on-cartridge sample preparation and detection. Multiple detection modalities including fluorescence and absorption will be supported along with thermal control. The FINDER platform and assays are in development. Time to result will be < 15 minutes according to the company. Baebies is in early development, adding nucleic acid testing to the platform with DNA amplification and integrated sample preparation.

c. Platform: spinit® / Manufacturer: biosurfit

Location	Azambuja, Portugal
Website	http://biosurfit.com/
Time to Market	On market; CE-IVD

Technology Overview
Centrifugal microfluidic platform integrated inside a plastic DVD-like disc and operated by rotation using a standard DVD drive. Immunoassays are performed with Surface Plasmon Resonance, cytology performed using an integrated microscopy module and standard hematology dyes. Clinical chemistry assays are performed by measuring the absorbance of light at different wave-lengths using multiple LEDs.

Assay Specifications	
Turnaround Time	4-12 minutes
Sample Processing	Fully integrated on-cartridge
Sample Types	Whole blood
Sample Volume	0.005 – 0.015 mL
Multiplexing	6 targets
Assay Types	Cell counting, immunoassays & clinical chemistries

Source: http://biosurfit.com/

Company background:
biosurfit is an early stage, privately held diagnostic company located in Azambuja, Portugal. The spinit® platform is designed to perform hematology, immunoassays and clinical chemistry on the same instrument at the point of care. Current assays that are CE-IVD marked include HbA1c, Blood Count (total leukocyte/5-part differential WBC/hematocrit), and quantitative C-reactive protein (CRP). In the pipeline is a multiplex assay for lipids (cholesterol, HDL, LDL, triglycerides, non-HDL, cholesterol/HDL ratio). biosurfit previously participated in a €6M EC POC HCV Consortium to develop tests for hepatitis C for resource limited settings along with Epistem.

Technology overview:
The spinit platform is a centrifugal microfluidic platform that uses three different technologies: immunoassays are performed with surface plasmon resonance using a polarized laser beam; hematology assays are performed using an integrated microscopy module using standard dyes; and clinical chemistry assays are performed by measuring the absorbance at multiple wave lengths using LEDs. Sample preparation is integrated in a disposable microfluidic plastic DVD-like disc that is operated by rotation using a standard DVD drive. Samples include whole blood (venous and capillary), serum and plasma. The system is capable of quantitation for all classes of analytes detectable by the platform and can multiplex up to six

targets. Sample volumes range from 5-15 µL for currently available assays. The time to result ranges from 4-12 minutes.

d. Platform: BLINK ONE / Manufacturer: BLINK AG

Location	Jena, Germany
Website	http://www.blink-dx.com/
Time to Market	Early access for 3rd party developers in Q3 2019

Technology Overview
BLINK ONE is a mobile, battery operated system with integrated liquid handling on a cartridge, rapid thermocycling and multi-color fluorescence imaging in combination with novel reagents facilitating sensitive, multiplexed detection of a broad range of analytes (nucleic acids, proteins, cells). The platform is being designed for use in primary health care settings.

Assay Specifications	
Turnaround Time	Unknown
Sample Processing	Fully integrated on-cartridge
Sample Types	Many different types including whole blood
Sample Volume	0.010 to 10 mL
Multiplexing	High multiplexing capability
Assay Types	Molecular, immunoassay & cell-based

Source: http://www.blink-dx.com/

Company background:
BLINK AG is a start-up company with more than 30 employees, located in Jena, Germany, and was founded in 2015. BLINK is developing the BLINK ONE product platform, a mobile, battery-operated system designed for use in level 1, or primary health care, settings. The technologies underlying the platform allow detection of a wide range of analyte types, including proteins, nucleic acids and cells. BLINK is exploring ways to establish local diagnostic service providers as operators of the platform. BLINK is also interested in an open business model to engage specialized IVD developers to develop different tests for use on the BLINK ONE platform. BLINK is in an advanced breadboard prototype development phase.

Technology overview:
BLINK's product architecture is based on a set of technology modules that facilitate safe liquid handling, reagent storage, rapid thermocycling, multi-color fluorescence imaging and multi-analyte detection of DNA, RNA, proteins and cells. One core aspect is digital detection of single molecule interactions. The product platform is designed to support development of new test assays through third party developers. The development tool box comprises a set of bioanalytical technologies to enable a broad range of sample processing workflows for different analyte types, enabling ultra-sensitive assays for nucleic acid targets and protein analytes with single molecule sensitivity, as well as cell-based and highly multiplexed assays. According to BLINK, "the technology is designed for processing sample sizes from a few µL up to large samples > 10mL and is compatible with all common sample matrices". No further information is publicly

available. BLINK is currently developing fully automated diagnostic tests for chronic myelogenous leukemia (CML) and for Hepatitis C Virus (HCV).

e. Platform: BluBox / Manufacturer: BluSense Diagnostics

Location	Copenhagen, Denmark
Website	https://www.blusense-diagnostics.com/
Time to Market	CE-IVD / on market

Technology Overview
Immuno-Magnetic-Assay (IMA) in combination with centrifugal microfluidics. Opto-magnetic detection of target molecules (antigens, antibodies, NAT) by measuring the change in dynamic rotation of magnetic nanoparticles (MNPs) upon specific cluster formation due to the analyte presence, using a Blu-Ray optical unit. Fully-automated sample processing and reagent manipulation is implemented in cartridge via centrifugal microfluidics.

Assay Specifications	
Turnaround Time	< 10 minutes
Sample Processing	None required, only dilution
Sample Types	Whole blood
Sample Volume	0.01 – 0.110 mL
Multiplexing	6 targets
Analyte Types	Immunoassay, molecular possible and early stage

Source: https://www.blusense-diagnostics.com/

Company background:
BluSense Diagnostics is a spin-off from the Technical University of Denmark, one of the leading technical universities in Northern Europe, with an international mix of founders and employees. BluSense is a startup with operations in Denmark (25 employees) and Taiwan (12 employees). They have established a global consortium of scientific and technological partners, with a strong footprint in South East Asia. The company has obtained several grant awards, including support from USAID under the Zika grand challenge and a grant from Horizon 2020 to support clinical validation and large-scale manufacturing of the dengue diagnostics technology.

Technology overview:
BluBox, the BluSense platform, is a centrifugal-based small benchtop platform for point-of-care blood testing that leverages Blu-Ray technology. BluBox is a readout platform for the immunomagnetic assay (IMA) format, a proprietary technology of BluSense Diagnostics. The technology, embedded in a multiplexed microfluidics cartridge, provides quantitative results in <10 minutes. The cartridges can multiplex up to six targets through geographic multiplexing via sample separation to up to six different detection chambers. However, all the current products in development have demonstrated only two or three targets on a single cartridge. Sample volumes vary by assay and range from 10 to 110 µL. All reagents are contained on the cartridge and no sample preparation is required, though some antibody assays may require a dilution step. BluSense envisions the BluBox to include cloud-based data analytics to analyze results and enable automated case reporting, but this capability is still in development. The company has certified its first dengue test (acute biomarker NS1) and it's clinically validating a specific immunoglobulin G and M for dengue, Zika and chikungunya tests. BluBox has demonstrated detection of hemoglobin A1C for diabetes

monitoring, CRP and the alkaline phosphatase (ALP) enzyme. BluSense is in the early stages of developing molecular detection capabilities on their BluBox using isothermal amplification (Rolling circle and LAMP), which leverages the same opto-magnetic bead readout as their immunoassay platform. Sample processing is performed off cartridge and this technology is in early stages of development. The BluSense platform and dengue test achieved CE-IVD in June of 2018.

f. Platform: LightDeck® Technology / Manufacturer: MBio Diagnostics

Location	Boulder, Co, USA
Website	http://www.mbiodx.com/
Time to Market	Platform on market for environmental testing applications only

Technology Overview
Combines planar waveguide-based illumination, microarray technology, microfluidics, and fluorescence imaging; quantitative. Sensitivity equivalent to ELISA.

Assay Specifications	
Turnaround Time	< 10 min (reading only)
Sample Processing	Not integrated
Sample Types	Whole blood, serum, plasma
Sample Volume	Depends on sample type
Multiplexing	High multiplexing: "up to 60 + controls"
Assay Types	Molecular, immunoassays, & cell counting

Source: http://www.mbiodx.com/

Company background:
MBio Diagnostics is a privately held company, founded in 2009, based in Boulder, Colorado, USA. It is a spin-off of the laser optics company Precision Photonics, which was purchased by Idex Corporation. MBio's LightDeck® platform is an analytical technology capable of performing quantitative immunoassays and cell-based assays. The company aims to be "the platform of choice for on-the-spot testing across industries and applications including users of clinical and analytical testing services in all market segments including: medical, veterinary, environmental, food, agricultural and military." MBio is focused on manufacturing and selling instruments and pursuing a licensing and OEM supply business model with regards to assays and applications.

MBio has published multiple application studies using its technology, including tests for CD4 T cell counts at the point of care and immunoassays for HIV, hepatitis and syphilis. They have received grant and contract awards by both DARPA and NIH to develop multiplex POC assays for acute infection diagnosis and sepsis prognosis using host biomarkers.

Technology overview:
MBio's "LightDeck®" is a multiplexed immunoassay system based on planar waveguide technology and fluorescence imaging. Samples are added to a disposable injection-molded plastic cartridge containing microarrays and lyophilized reagents. Cartridges can be configured to run "dozens of parallel assays from a single sample" and up to 60 analytes plus controls, according to one company presentation. Cartridges are

processed “off instrument” and then read in the instrument. The research instrument operates as a USB peripheral device, drawing power and communication via a laptop computer. A fully integrated reader with on-board computer and touchscreen is in development at the company. Sensitivity of the assays is similar to a standard multi-step, heterogeneous sandwich ELISA assay and results can be quantitative. MBio has demonstrated multiplexed immunoassays in 10 minutes (HIV) using whole blood, plasma or serum samples.

g. Platform: Evidence MultiSTAT / Manufacturer: Randox

Location	Crumlin, County Antrim, Northern Ireland, United Kingdom
Website	https://www.randox.com/evidence-multistat/
Time to Market	On market, CE-IVD

Technology Overview
Biochip Array Technology: enzyme labeled reagents catalyze a chemical reaction on a biochip which generates a chemiluminescent signal. Each biochip has up to 49 Discrete Test Regions (DTR). The light emitted from the chemiluminescent reaction that takes place in each DTR is simultaneously detected and quantified using a CCD Camera. This platform is focused on drug screening.

Assay Specifications	
Turnaround Time	17 minutes
Sample Processing	Not required
Sample Types	Milk, urine, whole blood, oral fluid, and a “wide range of forensic matrices.”
Sample Volume	
Multiplexing	44 + controls
Assay Types	Immunoassays

Source: https://www.randox.com/evidence-multistat/

Company background:
Randox is a large, privately held company located in Crumlin, County Antrim, Northern Ireland, UK. Major R&D and manufacturing sites are also located in Bangalore, India and the Washington DC area, USA. Randox manufactures and markets instruments and assays for life science, research, food testing, forensic, veterinary, and human diagnostic laboratories. They have worldwide distribution. In diagnostics, they have centralized laboratory instruments and assays in clinical chemistry, molecular, immunoassays, drugs of abuse, cardiac monitoring, and therapeutic drug monitoring. Randox has also entered a partnership with the German engineering firm Bosch to provide molecular assay content for their molecular platform for near patient testing called Vivalytic, due for release in early 2018.

Randox manufactures four different immunoassay analyzers for different lab sizes—all are called “Evidence.” These analyzers all use an array-based format that enables multiplexing using their microarray and chemiluminescence technology. The Evidence MultiSTAT is Randox’s POC immunoassay analyzer. Available tests on this platform include drugs of abuse, veterinary drug residues (food), toxicology and clinical diagnostic assays.

Technology overview:
The Evidence MultiSTAT immunoassay instrument uses Randox's patented "Biochip Array Technology" coupled with chemiluminescence output. Each biochip has up to 49 discrete test regions" that can be labeled with different ligands. This enables multiplex testing of up to 44 analytes plus internal controls. Immunoassays use enzyme labeled chemiluminescence detected and quantified using a CCD camera. Applications are available for milk, urine, whole blood, oral fluid, and a "wide range of forensic matrices." MultiSTAT is a benchtop instrument designed for POC, non-laboratory settings that tests a single sample at a time. Each sample has an assay turnaround time of less than 20 minutes and uses two cartridges to eliminate sample carry-over. The reagent cartridge contains all the liquid reagents required to complete the test cycle while the tip cartridge houses the disposable tips and also collects the liquid waste generated by the system.

h. Platform: TBD (POC system in development) / Manufacturer: Singulex

Location	Alameda, California, USA
Website	www.singulex.com
Time to Market	POC system in early development

No graphic available for POC system

Technology Overview
Single Molecule Counting technology: sample containing analyte is combined with paramagnetic microparticles coated with capture antibodies and detection antibodies labeled with fluorescent dye. Single fluorescently-labeled molecules pass through a small interrogation space created by a confocal detection system that generate intense flashes of light as they are illuminated by a laser and read by confocal microscopic optics.

Assay Specifications	
Turnaround Time	5-10 minutes
Sample Processing	Fully integrated on-cartridge
Sample Types	Whole blood
Sample Volume	Unknown
Multiplexing	At least 3 targets
Assay Types	Immunoassays

Company background:
Singulex is a mid-sized, privately held company located in Alameda, California, USA (San Francisco Bay Area near Berkeley). Singulex has developed a centralized lab protein detection system -- Sgx Clarity™ System using their single molecular counting (SMC) technology. The Clarity system and assays have obtained CE marking and are commercially available in Europe. Cardiac troponin is currently available, and they are developing a *Clostridium difficile* toxin A/B and procalcitonin assay. The company submitted the instrument and troponin assay to the FDA in late 2017.

A major focus of the company is developing a point-of-care instrument version of their technology. Singulex has developed a prototype as of Q4 2017 and plans to eventually pursue CE-IVD and FDA clearance. They are working with Grifols Diagnostic Solutions, which invested $50 million in Singulex and owns a 20% stake in the company. Grifols is interested in using Singulex SMC technology for blood screening applications including immunoassays for HIV, hepatitis C virus, and hepatitis B virus.

Technology overview:
Singulex technology combines a microparticle-based immunoassay with digital SMC technology. A biological sample which contains the analyte of interest is combined with paramagnetic microparticles coated with capture antibodies and fluorescent-labeled detection antibodies. After incubation and washing, the complex is disrupted, and the fluorescent-labeled detection antibodies are analyzed using SMC technology. They pass through a confocal microscope detection system and are illuminated by a laser, generating flashes of light. The measured fluorescence is detected as a series of digital events, each representing a single fluorescent-labeled molecule. The fluorescent signal is translated into the concentration of the analyte in the sample. This technology enables assays with high sensitivity (low femtomolar) and broad dynamic range (6-log reporting range). Multiplexing capability is unclear. Published studies by Singulex demonstrate three analytes. The current centralized lab, Clarity system, is fully automated with a turn-around time of 90 minutes. There is no publicly available information on their POC system.

i. **Platform: LabDisk / Manufacturer: SpinDiag**

Location	Freiburg, Germany
Website	https://spindiag.de/
Time to Market	Forecast 2020 for CE-IVD molecular only product

Technology Overview
Centrifugal-microfluidic test system based on a disk using centrifugal force to perform reagent release, distribution of aliquots of the sample to different assay compartments and to drive the opening and closing of valves so as to generate the right sequence of mixing or splitting of the reagents and sample. Read-out is fluorescence-based.

Assay Specifications	
Turnaround Time	30 – 165 minutes
Sample Processing	Fully integrated on-cartridge
Sample Types	Nasal/rectal swabs
Sample Volume	0.2 mL – 1 mL
Multiplexing	~20 targets, more possible
Assay Types	Molecular & immunoassays

Source: https://spindiag.de/

Company background:
SpinDiag is a startup company located in Freiburg, Germany. It was spun off from the Hahn-Schickard Research Institute with US $1.9 million in seed funding and recently closed a US $3.5 million Series A. Hahn-Schickard is a private, non-profit engineering and research organization, which has a strategic alliance with the IMTEK-Department of Microsystems Engineering, University of Freiburg, Germany. The SpinDiag technology includes the LabDisk cartridge and LabDisk reader, both developed by scientists and engineers at Hahn-Schickard with multiple collaborators as part of several European Commission (EC) and German Federal Ministry of Education and Research (BMBF)-funded infectious disease diagnostic projects, most notably the EC-funded DiscoGnosis project (www.discognosis.eu) (FP7 GA-318408) which ended in 2016 and the BMBF-funded NesDiag 2 project (031B0077A). SpinDiag is focusing on an initial rapid, POC molecular diagnostic platform targeting 25 of the most prevalent AMR markers in 30 minutes using a small, portable device platform “with a competitive price and inexpensive disposable cartridges for diagnostics directly from standard patient swab samples.” This would be a screening assay from a nasal/rectal swab for

MRSA, VRE, carbapenemase-producing organisms and partial coverage of ESBL. They are planning to complete development of their first product by the end of 2018, clinical validation in 2019 and early 2020 for CE-IVD and product launch. They also have plans for FDA clearance.

Technology overview:
The LabDisk system uses centrifugally operated microfluidics and a disposable cartridge disk similar to a CD that is made with injection-molded parts and "scales well in mass manufacturing," according to SpinDiag. They are currently not developing immunoassays for commercial launch, though the platform is capable of immunoassay detection. In addition to their NAT products in development, they have developed a complementary prototype protein biomarker and immunoassay LabDisk (different cartridge) that also can be processed with the LabDisk player. Assays for CRP and ricin have been prototyped and published and they claim that it is capable of antibody detection assays.

5. SUMMARY

In this report and associated spreadsheet, we have reviewed 54 immunoassay platforms and identified nine platforms of relevance to the MAPDx program as defined by its TPP.

5.1 Perspective: trends in immunoassay platforms

There is striking divergence between the current landscape of immunoassay platforms and that of molecular (NAT) platforms. This variation is important to understand, as this will have significant implications for the MAPDx program, as well as for MSF's strategy to identify potential industry partners. In contrast to the multiplex molecular landscape, there are considerably fewer multiplex immunoassay platforms that match the key characteristics of the MAPDx TPP: bench-top, multiplex, random access with multiple ports, integrated sample to answer, and ability to process large volume samples and complex matrices. The dissimilarities between the two landscapes are due to the fact that NAT and immunoassays exhibit key differences in fundamental principles essential to these diagnostic technologies (
Table 2).

Table 2: Comparison of key characteristics of immunoassay and nucleic acid testing systems

	Immunoassay systems	**Nucleic acid testing systems**
Multiplex, bench top, random access integrated systems	Few (competition, innovation in RDTs)	Many (accelerating competition & innovation)
Sensitivity measured in:	Concentration	Amount ("copies"/IU)
Specimen volume	Small volumes a feature (miniaturized)	Large volumes a feature (superior sensitivity)
Specimen matrices	Simple (serum, plasma)	Complex (sputum, feces, respiratory tract swabs)
Turnaround time	Short (usually minutes)	Long (often 1 hour or more)*

*Turnaround time can vary depending on the amplification chemistry, sample types, and the target analytes and their relative concentration in the sample. In some cases, some molecular tests can have much faster turnaround times.

Immunoassay platforms vs molecular platforms
Immunoassay sensitivity is generally **analyte <u>concentration</u> dependent**, involving kinetic reactions of antigen and antibody; NAT sensitivity is dependent on **analyte <u>amount</u>** (stochastic reactions of nucleic acid

amplification). Because they are concentration dependent, **immunoassays can be successfully miniaturized**, and sensitivities are expressed in terms of molar concentration (e.g., femtomolar, picomolar). In contrast, NAT sensitivity is dependent on the amount of analyte present in the specimen; the target must be present for it to be amplified. NAT sensitivity is expressed in terms of “copies” or international units. As a result, small specimen volumes are a product feature for immunoassays, whereas for NAT, this is a weakness since the ability to process large sample volumes is critical to assay performance.

Furthermore, sample preparation is a critical step for NAT and is more complex in comparison to immunoassays because the performance of the test is dependent on the amount of high quality purified nucleic acid available for analyte amplification. In fact, much of the recent progress in NPT benchtop NAT systems has been enabled by companies developing engineering and chemistry innovations in sample processing.

Turnaround time is also different between immunoassays and NAT. It is possible for most immunoassays to be **completed in minutes**, whereas NAT frequently takes an hour or more. Because of this, **single cartridge/port systems are commonplace with immunoassay systems and provide sufficient throughput**. This is not the case with NAT systems, where multiple ports and random access are key product features. Immunoassays also generally require much less power consumption than NAT and are less likely to require a main power supply.

Implications for immunoassay platforms relevant to the MAPDx program

In contrast to the rapid innovation and competition occurring in benchtop molecular diagnostic platforms, we have identified far fewer immunoassay platforms (Figure 22). **Immunoassay technology innovation and market growth today is predominately in lateral flow/immuno-chromatographic** assays and not in benchtop systems. Lateral flow immunoassays can offer real advantages in that they are simple, low cost, and enable flexibility for regional panels. Their performance is generally “good enough” depending on the analyte of interest and comprise much of the immunoassay market. **Drivers for innovation and competition in immunoassay bench-top systems are limited to applications requiring very high sensitivity where lateral flow assays are inadequate (e.g., cardiac markers).** An example is the “single molecule” detection technology being developed by Singulex.

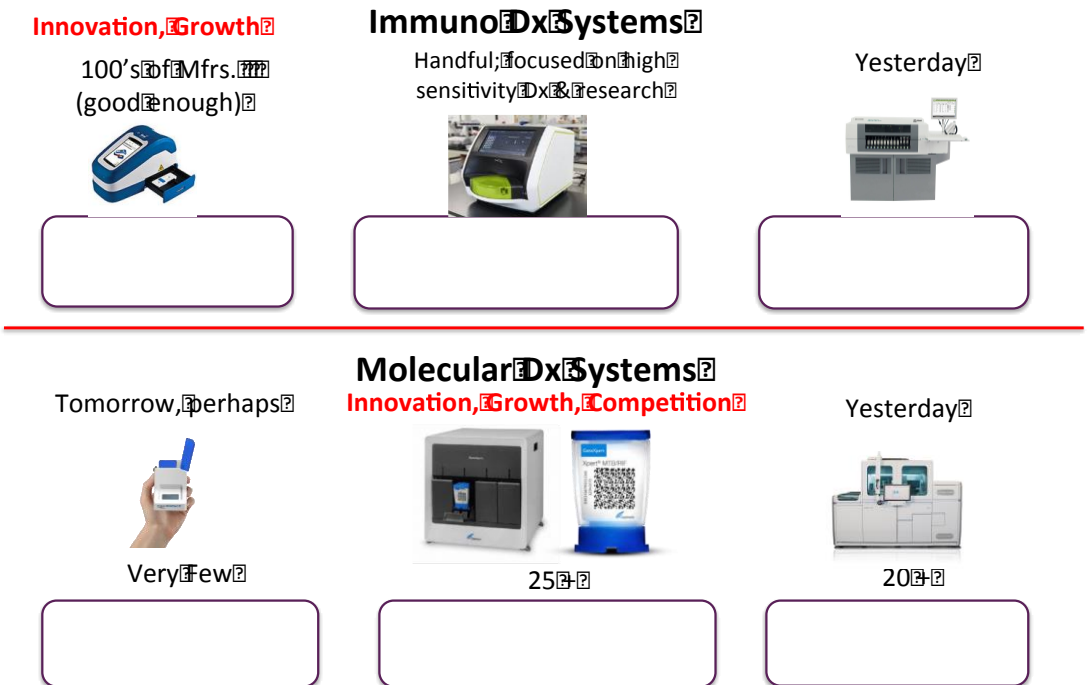

Figure 2: NAT and immunoassay landscapes: compare and contrast

5.2 Technologies of relevance to MSF's MAPDx program

The objective of the initial test panel for the envisioned MAPDx platform is to improve the ability of MSF clinicians to diagnose and manage patients presenting with severe febrile illness of unknown source. Existing commercial instruments are limited to detection of one analyte type or class (e.g., nucleic acid, protein, antibody) on a dedicated instrument. The MAPDx system would enable testing for multiple disease targets, reduce the need for numerous platforms, and advance diagnostic capabilities in RLS. Given that MSF's priority analyte types are nucleic acids and immunoassay targets, we compared the top nine immunoassay platforms by key attributes essential to the MAPDx platform, including analyte detection capabilities and critical company factors as detailed in Table 3 below. Technologies are listed in alphabetical order by manufacturer.

Table 3: Summary of key attributes immunoassay platforms of relevance to MAPDx

Manufacturer	Platform	Platform capabilities (Y – yes, M – some design features, N – no)					Other analyte detection capability (P - products available, C - system design is capable though no products available, N = no capability)			Estimated. time to launch
		Design for RLS	Integrated Design	Multiplexing (max # targets)	Design Format	Core Technologies	NAT	Clinical Chemistry	Cytometry	
Abionic	abioSCOPE	Y	Y	10	Centrifugal microfluidics	Fluorescent nanofluidics	N	N	N	Launched (CE-IVD, FDA)
Baebies	FINDER	M	Y	7	Digital microfluidics	Fluorescence or absorbance detection	C	P	N	< 3 years
biosurfit	spinit	Y	Y	6	Centrifugal microfluidics	Surface plasmon resonance	N	P	P	Launched (CE-IVD)
BLINK AG	BLINK BOX	Y	Y	TBD	Liquid handler	digital single molecule detection, fluorescence	C	N	C	< 3 years
BluSense Diagnostics	BluBox	Y	Y	5	Centrifugal microfluidics	Optomagnetic nanoparticle Blu-ray detection	C	N	N	Launched (CE-IVD)
Mbio	LightDeck	Y	N	60	Microarray	Planar waveguide, fluorescent imaging	C	N	C	< 3 years
Randox	Evidence MultiSTAT	N	M	44	Biochip array	Enzyme labeled chemi-luminescence	N	N	N	Launched (CE-IVD)
Singulex	POC platform (name TBD)	Y	Y	3	Paramagnetic microparticle	Digital single molecule counting	N	N	N	< 3 years
SpinDiag	LabDisk	Y	Y	20	Centrifugal microfluidics	Magnetic beads, fluorescence	C	N	N	< 3 years

Conclusion

Although no platforms that are either commercialized or in development entirely satisfy the key product characteristics as described in the MAPDx TPP, several platforms incorporate essential design elements of the MAPDx vision. It is technically feasible that some of the technologies identified in this landscape as well as those identified via the molecular landscape could achieve the envisioned MAPDx product requirements through a dedicated product development effort. Any of these platforms will require significant investment, engineering and assay optimization/innovations to meet the specifications described in the TPP. The extent of this product development effort will depend on the level of core technology demonstration and platform integration. In many cases, characteristics for environmental conditions typical in areas where MSF works will require specialized designs, since the majority of technologies have not been designed for use in the extreme operating conditions commonplace in resource limited settings.

6. LIMITATIONS

All landscapes are a snapshot in time and are not living documents. The content provided in this report reflects publicly available information collected during Q3 2017 through Q1 2018. Furthermore, companies reviewed their company content for accuracy during Q3 2018 and in some instances, updated figures were provided.

7. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

8. APPENDIX

8.1 Attachment 1 – MAPDx TPP

A multiplex multi-analyte diagnostic platform

Introduction

Fever is one of the most common reasons for admission to hospitals in low-resource settings.[1,2] Among the millions of patients Médecins Sans Frontières (MSF) sees each year, the problem of patients presenting with severe febrile illness without a known source[3] is frequent. Treating these patients poses a significant challenge due to a lack of reliable and comprehensive diagnostics.

Meeting broader global health needs

The problem of severe febrile illness has led MSF to call for a new diagnostic paradigm: development of a multiplex and multi-analyte pathogen diagnostic (MAPDx) platform. MAPDx would comprise an instrument platform with assay cartridges designed to detect a broad range of pathogens. While MSF's initial goal is focused on clinical care at the referral level for diagnosing severe febrile illness without a known source, the design of the platform would support the development of assays for many other illnesses, including HIV, TB and malaria, as well as assays for non-communicable diseases, such as diabetes.

Fostering business innovation

The programme is intended to stimulate the development of a semi-open business model for MAPDx. Several variations for a semi-open business model can be envisioned; however, at its base, this model is founded on a partnership between the manufacturer of record (MoR) and partners who support the business by either designing and/or manufacturing assays and cartridges. In one example, a single manufacturer designs, develops and manufactures the platform as MoR. The MoR would also design the compatible cartridge required for the assays to be run on the instrument. The MoR, or a subcontractor, would manufacture the open cartridge and make it available to trusted assay development partners. Assay development partners would design compatible assays using the MoR's assay development toolkit. MSF's ultimate goal, once certain volume milestones have been met, is to arrive at a fully open business model for MAPDx where multiple platform and cartridge manufacturers would be available in the market.

The intent of the semi-open business model is to stimulate a broader and more flexible partnership between industry partners, such that multiple assay developers have the ability to design and offer tests on a platform instrument. This could in turn enable implemented platforms to have a breadth of applications to allow the testing facility to cover multiple diagnostic needs while investing in fewer instruments.

Developing a target product profile

MSF and FIND partnered with the World Health Organization (WHO) to conduct a consensus target product profile (TPP) development process for MAPDx, consisting of an instrument and a generic assay cartridge. The purpose of a TPP is to inform product developers of key characteristics and performance specifications required to meet end user needs for a defined use case. TPPs often include an optimal and a minimal

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[1] Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. The Lancet infectious diseases 2010; 10:417–32.

[2] Crump JA, Gove S, Parry CM. Management of adolescents and adults with febrile illness in resource limited areas. BMJ (Clinical research ed.) 2011; 343:d4847.

[3] Febrile illness, independent of duration (acute and persistent), without evidence of localized infection by history, physical examination, and appropriate diagnostic tests and severity identified by danger signs

definition for each performance characteristic. Ideally, products should be designed to achieve as many of the optimal characteristics as are feasible, while still satisfying the minimal criteria for all defined features.

An overview of the entire TPP development process is summarized in Figure 1 below. To develop a draft TPP for this diagnostic platform, key stakeholders and experts were interviewed, and a TPP working group developed a working draft TPP. To leave open the possibility of techniques not yet considered, this draft TPP is agnostic to the precise technology required. Moreover, it envisions a platform that can perform a wide variety of tests, depending on the assay cartridge used.

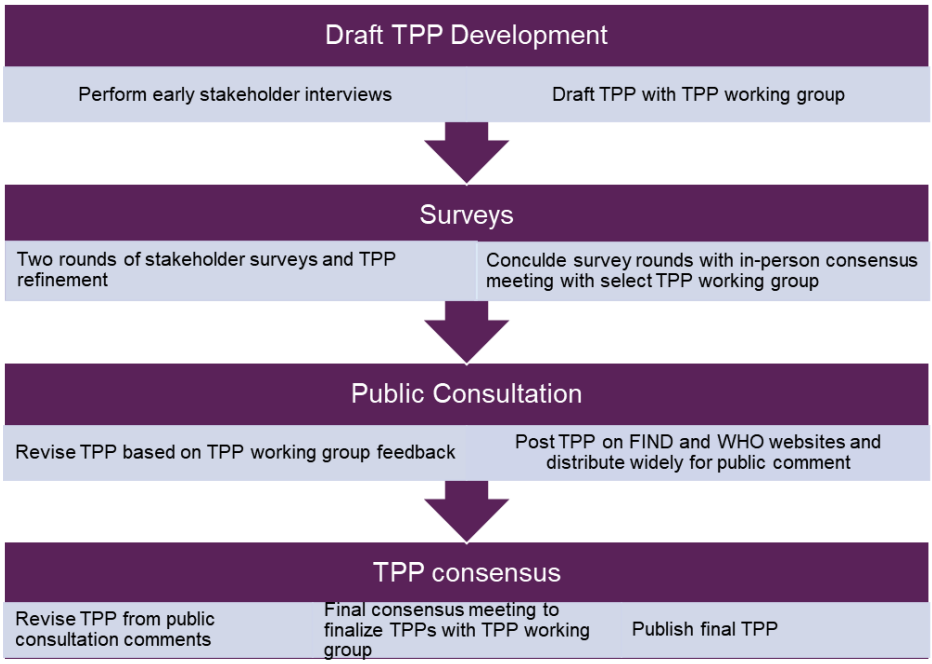

Figure 1: Overview of the TPP development process

Delphi-like process

To obtain consensus and arrive at a final TPP for MAPDx, a Delphi-like process was followed enlisting stakeholder input from 52 content experts. Stakeholders were surveyed electronically to obtain input on all 41 TPP characteristics. Survey participants were asked to rank their level of agreement based on a Likert scale ranging from 1 to 5 (1-disagree, 2-mostly disagree, 3-don't agree or disagree, 4-mostly agree, 5-fully agree). Individuals were asked to provide comments when they scored a characteristic at 2 or lower. Consensus was pre-specified as >50% of responders agreeing with the proposed characteristics (Likert score of 4 or 5). A second level of consensus was evaluated at >75% agreement. Responses were analysed separately for industry and non-industry responses. Responses were collated, and revisions were discussed by the TPP working group to address survey respondent concerns for those characteristics with lower levels of agreement. The revised TPP was sent for a second Delphi survey round and the process was repeated.

A TPP consensus meeting, co-hosted by FIND, WHO and MSF, was held on 25 October 2017, in Geneva, Switzerland. This consensus meeting included a select group of experts with extensive and relevant field experience. TPP characteristics from the second Delphi survey that had lower levels of agreement (6 characteristics) were discussed. Survey comments were discussed and revisions to the TPP were drafted during the meeting and agreed upon by voting participants (n=13). Voting was based on a super majority,

with a 70% threshold. During the consensus meeting, revisions to the TPP were completed and full consensus was achieved on all but two characteristics, which exceeded the 70% super majority threshold.

Following the consensus meeting, the revised draft was put forward for a month of public consultation on the WHO and FIND websites. Respondents (n=8) were asked to rank their agreement or disagreement with each characteristic and offer comments on each section of the TPP. There were high levels of agreement and minor changes were made to two characteristics as agreed by the TPP working group. The final consensus-derived TPP is detailed below.

Conclusion

As noted above, the instrument and cartridge described in the MAPDx TPP is meant to be “generic” so that it can meet a wide variety of diagnostic needs. MSF and FIND will leverage the MAPDx TPP as a foundational document to develop a fever-specific assay TPP.

MSF, FIND, and WHO strongly believe that the development of a concise and well-vetted TPP for MAPDx can accelerate technological advances that will have a significant impact on global health. Other interested parties are invited to create other pathogen or syndrome-specific TPPs based on the instrument and cartridge described herein.

Target product profile for a multiplex multi-analyte platform diagnostic (MAPDx)

	Characteristic	Minimum requirement	Optimal requirement
Scope of the platform			
1	**Intended Use**[4]	In the context of infectious diseases, intended for individual patient management of patients presenting with symptoms consistent with severe febrile illness without a known source[5]	Same, plus offering an expanded test menu to increase market size for product sustainability[6]
2	**Description of System**	The system will consist of an instrument[7] designed for use in combination with a self-contained, disposable assay cartridge(s)[8] containing all required reagents to execute a test from sample to result	
3	**Target Use Setting**	Level 2[9] Healthcare Facility (District Hospital or above) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust, and medical staff onsite. The target use setting does not include mobile testing facilities	Level 1[9] Healthcare Facility with rudimentary staffed/equipped laboratory, inconsistent electricity, including frequent surges and/or outages, no climate control, dust, but trained medical staff on-site for result interpretation and patient management
4	**Target User**	Trained laboratory personnel (e.g., 1–2 year laboratory training certificates)	Minimally skilled healthcare personnel (e.g., 3–6 months laboratory training, able to operate an integrated test with minimal additional steps)
Instrument			
5	**Instrument Design**	Single integrated instrument with universal port(s) capable of interfacing with one or more cartridge designs for simultaneous detection of multiple analytes to achieve the intended use	
6	**Size**	Small, table-top instrument (50 cm x 75 cm by 50 cm, or smaller)	
7	**Weight**	≤25 kg	≤10 kg

[4]Ghani AC, Burgess DH, Reynolds A, Rousseau C. Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. *Nature* 2015;528:S50-52

[5] Severe febrile illness without a source is defined as "Febrile illness, independent of duration (acute and persistent), without evidence of localized infection by history, physical examination, and appropriate diagnostic tests and severity identified by danger signs"

[6] Including uses to improve public health

[7] Instrument is used throughout the document; however, any innovative design/embodiment that meets the described characteristics is acceptable

[8] Assay cartridge is used throughout the document; however, any innovative design/mechanism that meets the described characteristics is acceptable

[9] Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing Harmonization and Standardization. 2008.

	Characteristic	Minimum requirement	Optimal requirement
8	**Power Requirements**	Local 110-220 AC mains power, plus uninterruptable power supply (UPS) to complete current cycle. UPS and circuit protector must be integrated within the system	Same, with rechargeable battery back-up (8-hour operation)
9	**Throughput**	Random access[10] required[11]with throughput up to 8 sample runs per instrument per 8-hour day	Random access required[9] with throughput up to 40 sample runs per instrument per 8-hour day
10	**Environmental Stability – Operating Range of Platform**	Operation at 10–35°C and up to 90% non-condensing humidity at altitude up to 2,500 meters. Able to function in direct sunlight and low light. Able to withstand dusty conditions	Operation at 5–45°C and up to 90% non-condensing humidity at altitude up to 3,000 meters. Able to function in direct sunlight and low light. Able to withstand dusty conditions
11	**Biosafety**	Closed, self-contained system; easy decontamination of instrument surfaces	
12	**Training**	<2 days training for skilled laboratory staff	<1 day training for minimally skilled staff
13	**Service, Maintenance and Calibration**	Daily preventive maintenance can be performed by laboratory staff in <30 minutes (with hands on time <10 minutes). Mean time between failures of at least 24 months or 10,000 tests, whichever occurs first. Self-check alerts operator to instrument errors or warnings. Need for instrument calibration onsite on a yearly basis by minimally trained technician	Routine preventive maintenance no more than 30 minutes 1x per week (with hands on time <10 minutes). Mean time between failures of at least 36 months or 30,000 tests, whichever occurs first. Self-check alerts operator to instrument errors or warnings; and ability to be calibrated remotely, or no calibration needed
14	**Patient Identification Capability**	Manual entry of alphanumeric patient identifier keypad or touchscreen compatible with protective gloves	Same, plus bar code, RFID or other reader
15	**Result Readout**	Quantitative based on the analytes of detection. Qualitative result available to user where that result is sufficient to inform clinical decision-making. Ability to select which test results are reported to the user based on the intended use in the regional epidemiological context in which the test is applied	
16	**Data Display**	On-instrument visual readout with ability to function in various lighting conditions ranging from direct sunlight to low ambient light conditions. Able to add information (patient ID, operator ID, date, location, etc.)	
17	**Connectivity**	• Integrated Local Area Network (LAN) port	Same as minimal, plus:

[10] Random access refers to the capability of the device to perform any test in any sequence at any time, with no interdependence on other test runs

[11] Note – no random access is required if time to result is less than 30 minutes

	Characteristic	Minimum requirement	Optimal requirement
		• Integrated Wi-Fi 802.11b/g/n • USB 3.0 • Internally designatable static IP address • Support for DHCP issued IP addresses • Support for HTTPS and SFTP protocols • Ability to update connectivity software stack via USB or LAN	• Multi-band GSM chipset 2G, 3G, LTE • Integrated Bluetooth 5.0 • Integrated Wi-Fi 802.11ac • Bi-directional communication – ability to update connectivity software stack
18	**Data Export**	Export of all instrument and test data over integrated hardware. Secured data export with end-to-end encryption. Data export in CSV file format. Configurable destination IP and DNS address. User initiated data export. Connectivity to external printer.	Same as minimal, plus scheduled/automatic data export using interoperable standards via GSMA SMS.
19	**Manufacturing**	ISO 13485:2016 compliant	
20	**List Price[12] of Instrument**	≤$15,000 (USD)	≤$5,000 (USD)
	Assay cartridge		
21	**Description of Assay Cartridge**	Self-contained, disposable cartridge(s) compatible with the universal cartridge port(s) of the instrument, containing all required reagents to execute a test from sample input to result. The assay cartridge will meet universal, 'semi-open'[13] design specifications made available by the manufacturer of the multiplex diagnostic platform to selected assay developers worldwide for use on such platform	
22	**Analytes**	Ability to simultaneously detect multiple analyte types (e.g. nucleic acids and serologic markers [antibodies, antigens and host biomarkers]) to achieve the intended use at the same	Ability to simultaneously detect multiple analyte types (e.g. nucleic acids and serologic markers [antibodies, antigens and host biomarkers]) to achieve the intended use at the same time, from a single specimen, in a single assay

[12] List Price– the price the manufacturer has arrived at for the product, taking into account the cost of goods and other factors (e.g., margin); the list price does not include any volume or other discounts or potential markup for distribution or other costs, including freight, taxes, etc.

[13] The semi-open system will consist of three components:

1. **Instrument Manufacturer**: will design, develop, and manufacture the multiplex diagnostic instrument and design an open cartridge for use on it.
2. **OEM Cartridge Manufacturer**: will manufacture open cartridges to pre-designed specifications on behalf of the instrument manufacturer.
3. **OEM Assay Manufacturers (Multiple)**: will develop assays for the cartridge based on an assay developer's toolkit provided by the instrument manufacturer.

	Characteristic	Minimum requirement	Optimal requirement
		time, from a single specimen, in one or more assay cartridges	cartridge; additional analyte detection capabilities preferred (e.g. clinical chemistries, cell counts)
23	**Multiplexing Capabilities**	Ability to detect a minimum of 6 pathogens[14] at the same time, from the same sample, in one or more assay cartridges	Ability to detect a minimum of 15 pathogens at the same time, from the same sample, in the same assay cartridges
24	**Test Kit**	All materials required for the test, including the assay cartridge, reagents, buffers or other consumables to test one patient, included in individually packaged, self-contained kit	
25	**Additional Third-Party Consumables**	None, except for sample collection and sample prep (e.g., volumetric pipettes)	None; cartridges contain all required reagents
26	**Specimen Type**	Ability to accept whole blood, serum, plasma, urine, cerebral spinal fluid and nasopharyngeal swabs, as required	Ability to accept all specimens in the minimum requirement as well as additional sample types, including sputum, saliva, stool, and various specimen swabs (i.e. rectal, vaginal, oral), and ability to use inactivated specimens, as required
27	**Sample Volume**	The minimal sample volume required to reach clinically relevant sensitivities, which in some cases could require up to 5 mL[15]	
28	**Sample Preparation**	Minimal sample processing. No more than 3 steps (requiring operator intervention). No more than 1 precision step (e.g., volumetric pipetting). Centrifugation or other off-cartridge sample processing steps acceptable	All sample processing steps are self-contained and performed within the assay cartridge. No precision steps required to be performed by the user
29	**Limit of Detection in Multiplex Format**	Equivalent or improved relative to reference assays (where available) for similar target analytes	
30	**Cross Reactivity**	No relevant cross-reactivity with microorganisms outside of the scope of the pathogens of interest, i.e. targets should be designed to not cross-react with other species within a genus or species that could be considered contaminants within the laboratory environment (e.g., *Staphylococcus aureus* vs. *Staphylococcus epidermidis*)	
31	**Interfering Substances**	No interference for an individual or mixtures of analytes due to interfering substances	
32	**Test Result**	Quantitative result based on the analytes of detection. Qualitative result available to user where that result is sufficient to inform clinical decision making	
33	**Time to Result**	<90 minutes	<30 minutes

[14] Assuming one or more analytes or assay targets per pathogen are required

[15] Volume requirements could be circumvented by off-cartridge processing steps as defined in the sample preparation characteristic

	Characteristic	Minimum requirement	Optimal requirement
34	**Controls – Internal Process**	A full internal process control must be integrated into the assay cartridge and the instrument	
35	**Controls – Positive/Negative**	External positive and negative controls are not required for each test but are performed daily	External positive and negative controls are not required for each test and do not need to be run daily
36	**Environmental Stability - Transportation**	No cold chain requirements. Stable at 2–45°C for up to 7 days, can tolerate short term temperature fluctuations from 0–50ºC. Up to 90% non-condensing humidity for up to 7 days	No cold chain requirements. Stable at 2–45°C for up to 15 days, can tolerate short term temperature fluctuations from 0–50ºC. Up to 90% non-condensing humidity for up to 15 days
37	**Environmental Stability – Operating Range**	10–35°C	5–45°C
38	**Waste/Disposal Requirements**	Direct disposal or incineration of consumables	Same, and no use of cyanide-containing reagents
39	**Shelf Life and Storage Conditions**	12 months, 70% humidity from date of manufacture (based upon real-time/accelerated stability studies) at up to 30°C	18 months, 95% humidity from date of manufacture (based upon real-time/accelerated stability studies) at 40°C
40	**Manufacturing**	ISO 13485:2016 compliant	
41	**List Price of Assay Cartridge[12]**	≤$15 (USD) at volume production	≤$5 (USD) at volume production

# # #

8.2 Attachment 2 – Full list of technologies included

Companies are listed in alphabetical order

	Manufacturer	Platform
1	1Drop Diagnostics	1Drop Reader
2	Abaxis	(TBD)
3	Abionic	abioSCOPE
4	AgPlus diagnostics	Ag+ reader
5	Alveo Technologies	(TBD)
6	Anvajo	MiniLab
7	ArcDia	mariPOC
8	Atlas Genetics Ltd	io™ multi-test system
9	Axela (Angle Biosciences)	Ziplex¨ System
10	Baebies	Finder
11	Biosenoryx	Stack Pad[a]
12	Biosensia	RapiPlex
13	biosurfit	Spinit
14	BLINK Dx	BLINK Box
15	BluSense Diagnostics	BluBox
16	Chembio Diagnostic Systems	Chembio products
17	ChipCare	Polyvalent Analyzer (PAx)
18	Coris BioConcept	Trapist V6
19	Danaher (Cepheid)	GeneXpert/GeneXpert Xpress
20	Danaher (Cepheid)	Omni
21	Edan	m16
22	Eurolyser Diagnostics	CUBE-S
23	Eurolyser Diagnostics	smart 700/546
24	Fluxergy	Search Light
25	Fujifilm	IMMUNO AU10V
26	Genspeed	Genspeed R-2
27	INT (Integrated Nano-Technologies)	Palladium System

28	MBio Diagnostics, Inc.	LightDeck Technology
29	miDIAGNOSTICS	miLAB
30	MIDS Medical	MIDS Cardiac
31	Mitsubishi	PATHFAST
32	NanoDetection Technology	No platform name
33	NanoIVD, Inc.	NanoIVD Clinical Analyzer I
34	Nanōmix	eLab
35	OPKO Health	Claros 1
36	Optolane	(TBD)
37	Ostendum	Ostendum platform
38	Philips	Minicare I-20
39	Pinpoint Science Inc.	(TBD)
40	Quanterix	SR-X
41	Radiometer Medical	AQT90 FLEX Immunoassay Analyzer
42	Randox	Evidence MultiSTAT
43	rHEALTH	rHEALTH ONE
44	Samsung	LABGEO IB10
45	SensoDx	SensoDx Platform
46	Siemens Healthcare	Stratus CS
47	Siloam Biosciences	TROVA
48	Singulex	"POC Platform"
49	SlipChip	SlipChip
50	SpinChip Diagnostics	SpinChip
51	SpinDiag	LabDisk
52	STAT-DX	DiagCORE
53	T2 Biosystems, Inc	T2MR
54	Two Pore Guys	(TBD)