Landscape of molecular platforms for near-patient testing: the MAPDx Program

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Authors:
Peter J. Dailey
Jennifer Osborn

Lead Reviewer:
Cassandra Kelly-Cirino

FIND
Campus Biotech
Chemin des Mines 9
1202 Geneva
Switzerland
T: +41 (0)22 710 05 90
F: +41 (0)22 710 05 99
www.finddx.org

Contents

ABBREVIATIONS

AMR	Antimicrobial resistance
CE-IVD	European CE Marking for *In Vitro* Diagnostic Devices
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
EC	European commission
FDA	Food & Drug Administration
FIND	Foundation for Innovative New Diagnostics
HRS	High resource settings
LRS	Low resource settings
MAPDx	Multi-analyte pathogen diagnostic
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
TPP	Target product profile
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Introduction

The Febrile Illness Diagnostic Programme, hosted by Médecins Sans Frontières (MSF) USA, has been examining the feasibility of developing a novel diagnostic (MAPDx) platform capable of simultaneously testing multiple pathogens and different analyte types to improve diagnosis and management of 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 on the same platform from the same sample. To identify technologies of interest and relevance to the MAPDx program, FIND conducted a landscape of molecular platforms that are either commercially available or in development and assessed them for their relevance to the MAPDx TPP. A complementary landscape was also conducted for immunoassay platforms during the same time period.

Through a comprehensive technology search conducted from Q3 2017 through Q1 2018, 107 molecular platforms were identified, and key technology features were compared to the MAPDx TPP (Appendix 1). The eleven platforms most closely matching the TPP are listed in alphabetical order by manufacturer in Table 1 in Section 4.

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, the capability to detect multiple analyte types (e.g., nucleic acids and immunoassay targets) on the same platform
- Technologies exist that demonstrate the feasibility of the MAPDx vision
- However, such 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 identified eleven molecular platforms with key attributes of relevance to the MAPDx program. Further details and evaluations of each of the platforms are provided below.

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 multiplex, multi-analyte diagnostic platform for near-patient testing (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 use 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 molecular platforms (either molecular only or platforms capable of molecular detection as well as other analyte classes/types) of relevance to the MAPDx program 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 MAPDx program.

Important Note: The objective of this landscape of molecular technologies is to address the requirements of the MAPDx TPP and is focused on the requirements of the MSF project. ***This is not a general landscape of molecular platforms.***

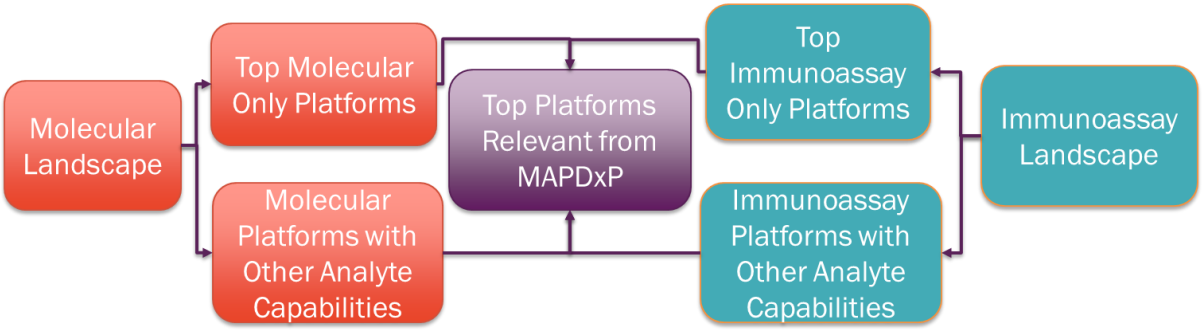


Figure 1: Overview of diagnostic landscapes to inform the MAPDx program

3. METHODOLOGY

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

1. Literature searches (search terms – “new, novel, comparison, and evaluation” used in combination with “molecular diagnostic, multiplex molecular diagnostic, nucleic acid test, polymerase chain reaction (PCR), isothermal amplification, Loop-mediated isothermal amplification (LAMP), platform, instrument”)
2. 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)
3. 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.
4. Attendance in-person at two 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)
5. Discussions with speakers, exhibitors, and consultants at SCASM and AMP from the following companies: DiasSorin Molecular, BioGX, Luminex, Abbott Alere, bioMérieux BioFire, Hologic, Cepheid, Quidel, GenMark, Roche Molecular Systems, Becton-Dickinson, Curetis, T-2 Biosystems, GeneStat, Qvella, ICubate, GenePOC, DNAe, XCR Diagnostics, and Vela Diagnostics.
6. Discussions with key opinion leaders and experts: Ellen Jo Baron (Diagnostic Microbiology Development Program, Cepheid), Michael Lewinski (Roche), Rick Nolte (Medical University of South Carolina), Steven Young (University of New Mexico, Tri-Core Laboratories), Nancy S. Miller, M.D. (Boston Medical Center), Melissa Miller (Univ. of North Carolina School of Medicine).
7. Diagnostic industry online reports and news (e.g., Genomeweb and Fierce Biotech)
8. Internet searches to identify multiplex molecular platforms
9. Antimicrobial resistance grant programs and “challenges” including the US National Institutes of Health/BARDA “Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test Challenge”, the United Kingdom “Longitude Prize”, CARB-X, and the CDC Innovations to Slow Antimicrobial Resistance.
10. Discussion with FIND team members, and recommendations from MSF staff

This comprehensive search identified 107 potential technologies. To identify key technologies of interest to the MAPDx program, the tools were evaluated based on FIND’s Technology & Partner Selection Guidelines, https://www.finddx.org/wp-content/uploads/2018/01/Tech-Partner-Selection-Guidelines_QP-02-08-02_V3.0.pdf. The tools were also compared with the MAPDx TPP specifications, and the top eleven diagnostic technologies were selected based on number of key features that satisfied the TPP requirements or that could be adapted to do so.

4. RESULTS

4.1 List of top tier companies

As a result of the first assessment, 107 platforms were shortlisted to the top 11 platforms of relevance to the MAPDx program. The technologies are listed in alphabetical order Table 1.

Table 1: List of top molecular technologies of relevance to MAPDx

	Manufacturer	**Platform**
1	Abbott	m-PIMA Analyzer
2	binx health	binx health *io*™ multi-test system
3	bioMérieux*	BioFire FilmArray
4	BLINK AG	BLINK One
5	Cepheid	GeneXpert
6	Cepheid	Omni
7	Curetis N.V.	Unyvero
8	QIAGEN	QIAstat-Dx
9	Quidel Corporation	Savanna
10	Roche Molecular Systems	cobas® Liat® PCR System
11	SpinDiag	LabDisk

4.2 Top tier company information

Details of the top 11 companies are described below and have been reviewed by the companies. The technologies are in alphabetical order by manufacturer.

1. Manufacturer: Abbott / Platform: m-PIMA Analyzer

Location	Chicago, IL USA (Abbott)
Website	https://www.alere.com/en/home/product-details/m-pima-hiv-1-2-viral-load.html
Time to market	Launched, WHO prequal and CE-IVD

Technology Overview
Integrated platform for RT PCR with multiplexing capability designed for use in LMICs. The m-PIMA HIV 1/2 Detect is CE-IVD and WHO PQ'd for Early Infant Diagnosis from 25µl of whole blood or plasma. m-PIMA HIV 1/2 VL is now also CE-IVD and WHO PQ'd for viral load monitoring from a 50µl plasma sample that can differentiate and quantify HIV 1, group 0 and HIV-2.

Assay Specifications	
Turnaround Time	60 – 70 min (depending on assay)
Sample Processing	Integrated in cartridge
Sample Types	Whole blood, plasma
Sample Volume	0.025 – 0.05 mL
Multiplexing	> 100 targets
Analyte Types	Molecular

Company background:
Alere has become a wholly owned subsidiary of Abbott Laboratories, a public Chicago, Illinois, USA company. Renamed Abbott Rapid Diagnostics (ARDx), the company focuses on rapid point-of-care (POC) diagnostics for infectious disease, cardiometabolic disease, and toxicology and thus expands Abbott's product offering the POC market.

Technology overview:
The m-PIMA is a fully automated nucleic acid amplification testing platform that enables POC real-time PCR. The platform is robust, battery operated and intended for use in decentralized laboratory and resource limited settings. Detection and quantitation of the m-PIMA platform uses PCR and real time fluorescence detection based on competitive reporter monitored amplification (CMA) probe hybridization onto a probe array. Multiplex PCR and the detection of mutations by a melting curve analysis is possible on this system.

The first product offering is the m-PIMA Detect for early infant diagnosis, which uses 25 µL of whole blood to detect HIV in less than 60 minutes. The latest product is m-PIMA HIV 1/2 VL for viral load quantification using 50 µL of plasma to detect HIV viral load in less than 70 minutes. m-PIMA HIV 1/2 VL received CE-IVD in December 2018 and WHO prequalification in April 2019.

2. Manufacturer: binx health™ / Platform: binx health *io*® system

Location	Cambridge, MA, USA
Website	www.mybinxhealth.com
Time to Market	CE mark for CT/NG obtained April 2019

Technology Overview
The binx health io® system utilizes electrochemical detection technology and multiplexing capacity. Amplification is by PCR. Designed for CLIA waiver. Small footprint instrument.

Assay Specifications	
Turnaround Time	~ 30 min
Sample Processing	Integrated on cartridge
Sample Types	Vaginal swabs, male urine
Sample Volume	up to 0.5 mL
Multiplexing	Up to 24 targets
Analyte Types	Molecular

Company background:

binx health™ is a UK based company with offices also in Cambridge, MA, US. Cartridge manufacturing is carried out by Bespak that is owned by Consort Medical, major investors in the technology. binx is ISO 13485 certified and announced CE marking in February 2016 for its *Chlamydia trachomatis* assay and *io*® system. In January 2017, binx completed a $35 million Series D financing round, which funded clinical trials and further product development of the dual chlamydia/gonorrhea (CT/NG) assay and manufacturing line. In April 2019, the company received CE marking of its dual chlamydia and gonorrhea assay. The company recently completed a pivotal FDA clinical study for the CT/NG dual assay for clearance by FDA, which was announced by the company in August 2019. In August of 2017, the company received a two-year phase II contract of $2.6M from SBRI (Small Business Research Initiative) to expand its sexually transmitted infection test menu on the *io* system to a 4-plex test to aid in the diagnosis of some of the most common sexually transmitted infections (*Chlamydia trachomatis, Neisseria gonorroheae, Trichomonas vaginalis, Mycoplasma genitalium*) and to support the adoption of the CT/NG assay and system platform into UK sexual health clinics. The company recently completed an i4i (invention for innovation) program grant with St. George's Hospital, London to develop an assay for the diagnosis of gonorrhea and simultaneous detection of resistant/susceptible strains to the first-line antibiotic Ciprofloxacin with the aim to improve antibiotic stewardship and expand the treatment options available for gonorrhea infections.

Technology overview:

The *io* system comprises a small, low cost, easy to use instrument (and a test-specific single-use cartridge) that is a fully integrated system designed to meet CLIA waiver. 500 µL of an unprocessed patient specimen (female vaginal swab or male urine in DNA preservation medium) are added to the cartridge which is then inserted into the instrument. The user follows a few on-screen prompts to start the test, which is performed under complete instrument control, with no further user intervention required. A result is delivered in about 30 minutes with no user interpretation needed. The *io* system provides fully customizable user control settings, end-to-end specimen tracking, hospital/laboratory information system connectivity and an internal process control which is automatically performed with every test to verify the test result. Amplification is by PCR and detection of the

amplified DNA uses an electrochemically-labeled DNA probe. The proprietary detection system and cartridge architecture allow for high multiplexing capability, currently up to 24 analytes.

3. Manufacturer: bioMérieux / Platform: BioFire FilmArray

Location	Salt Lake City, Utah, USA
Website	www.biofiredx.com
Time to market	3 BioFire instruments and 5 syndromic panels with FDA clearance & CE marking

Technology Overview
The BioFire FilmArray platform is an FDA cleared, and CE marked in vitro diagnostic multiplexed PCR system. The system is full automated and performs sample preparation, nested multiplex PCR, data analysis and report generation.

Assay Specifications	
Turnaround Time	45 – 75 minutes
Sample Processing	Integrated
Sample Types	Multiple sample types depending on the panel (e.g. WB, respiratory and rectal swabs)
Sample Volume	0.2 mL – 0.3 mL
Multiplexing	High multiplexing capability (~100)
Analyte Types	Molecular

Company background:
BioFire, formerly Idaho Technology, Inc, is wholly owned by bioMérieux, a multinational in vitro diagnostics (IVD) company with headquarters in Marcy l'Étoile, France. After being acquired in 2014, BioFire was split into two subsidiaries: BioFire Defense, LLC, and BioFire Diagnostics, LLC. The corporate offices for both subsidiaries are located in Salt Lake City, Utah, USA.

BioFire Diagnostics manufactures and distributes the BioFire® FilmArray® System as a sample-to-answer infectious disease diagnostic system focusing on highly multiplexed syndromic panels. It's current portfolio of CE-IVD marked and FDA-cleared panels include the BioFire FilmArray Respiratory Panel (20-22 viral and bacterial pathogens), the BioFire FilmArray Blood Culture Identification Panel (24 bacteria, fungi, and 3 antimicrobial resistance markers), the BioFire FilmArray Gastrointestinal Panel (22 viruses, bacteria, and parasites), the BioFire FilmArray Meningitis/Encephalitis Panel (14 bacterial, fungal, and viral pathogens) and the BioFire FilmArray Pneumonia Panel (33-34 bacterial and viral pathogens, including 7 antimicrobial resistance markers). Each of these panels can be run on BioFire's proprietary instruments – the BioFire FilmArray 2.0 (1 to 8 modules) or the higher throughput BioFire FilmArray Torch System (2 to 12 modules). In the United States, BioFire Diagnostics also markets the BioFire FilmArray EZ Configuration (CLIA-waived) for near patient testing (1 module).

BioFire Defense develops assays for the military and biothreat markets, with some assays commercially available for non-military users. Commercially available tests include an FDA emergency use authorization FilmArray assay for Ebola virus (specimens; whole blood and urine) and a research use only highly multiplexed FilmArray Global Fever Panel (19 bacteria, viral, and protozoan pathogens; specimen: whole blood).

Technology overview:

The BioFire System automates the detection and identification of multiple pathogens directly from a single patient sample in a closed disposable reagent pouch. The tests takes about two minutes of hands-on-time, with a total run time of 45 minutes to about an hour (assay dependent). The process includes automated sample preparation, nested multiplexed nucleic acid amplification, DNA melting analysis and results generation. To start the test, rehydration buffer is added to the reagent pouch. The sample is mixed with a denaturing buffer which is then added to the pouch. Both rehydration solution and the sample/buffer mixture are automatically drawn into the pouch via vacuum with no measurement required. The pouch is inserted into the BioFire FilmArray instrument and the user starts the test and walks away. The instrument moves the sample though the reagent pouch to perform mechanical disruption of organisms, purification of nucleic acids, and nested multiplexed nucleic acid amplification (including reverse transcription for RNA targets). The products from the first stage PCR are moved to an array with approximately 100 wells pre-spotted with primers for second stage PCR. At the conclusion of nucleic acid amplification, amplicon melt curve analysis is used to confirm the identity of the target. The BioFire software interprets the results of the melt curve analysis and a report is automatically generated at the end of the run. The BioFire FilmArray has the potential to detect more than 100 different nucleic acid targets at one time. Most assays are qualitative; however, the BioFire Pneumonia Panel provides semi-quantitation results for 15 bacteria. The BioFire instruments also have the capability of being connected to several laboratory information systems for easy sharing of results.

4. Manufacturer: BLINK AG / Platform: BLINK ONE

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, located in Jena, Germany, is a start-up company founded in 2015 and today has more than 30 employees. 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).

5. Manufacturer: Cepheid / Platform: GeneXpert

Location	Sunnyvale, CA, USA
Website	http://www.cepheid.com
Time to market	FDA and CE-IVD products

Technology Overview
GeneXpert diagnostic systems enable integrated near-patient nucleic acid testing using PCR for applications in infectious disease, genetics, and oncology. There are over 20 FDA cleared or CE-IVD products available for this platform.

Assay Specifications	
Turnaround Time	30 min to 2 hours (depending on which assay)
Sample Processing	Integrated on cartridge
Sample Types	Whole blood, sputum and others
Sample Volume	0.1 - 2 mL
Multiplexing	Currently 6 targets (10 targets + melt in development)
Analyte Types	Molecular

http://www.cepheid.com

Company background:
Cepheid, located in Sunnyvale, California, USA, is a wholly owned subsidiary of Danaher Corporation (NYSE:DHR). Cepheid has 20 FDA cleared and 28 CE-IVD assays, the most for companies with integrated nucleic acid amplification testing, several of which are used predominantly in resource limited settings, including Xpert HIV Qual for early infant diagnosis, Xpert MTB/RIF Ultra and Xpert Ebola. Cepheid has developed infectious disease assays for healthcare-associated infections, respiratory infections, viral load assays, antimicrobial resistance surveillance, and sexually transmitted infections. Most assays can be completed in approximately 90 minutes or less, with some delivering answers in <20 minutes. Cepheid had extensive experience working in RLS with FIND during the development and rollout of the GeneXpert MTB/RIF assay. In 2016, Cepheid's Xpert Flu/RSV assay received a CLIA waiver followed by Xpert GAS (Group A streptococci) in 2018.

With the GeneXpert platform, Cepheid has the largest installed base of any molecular diagnostic company. They manufacture multiple instruments with a differing number of modules providing flexibility and scalability. All modules are essentially identical and process one test cartridge at a time. There are systems containing 1, 2, 4, 16 modules. The GeneXpert Infinity 48 and 80 are highly automated systems for large, centralized laboratories. There are two- or four-module systems, the GeneXpert Xpress II or GeneXpert Xpress IV, which are specifically CLIA-waived POC systems and the one-module system, the GeneXpert Edge that provides external battery to facilitate near patient testing.

Technology overview:
Cepheid's GeneXpert diagnostic systems enable integrated near-patient NAAT for infectious disease, genetics, and oncology. Sample preparation is a strength of the GeneXpert. The instrument contains an ultrasonic horn that interacts with glass beads to break up difficult targets such as *Mycobacterium tuberculosis* and bacterial spores (anthrax and *C. difficile*). All Cepheid assays use PCR for nucleic acid amplification. Variations that they have used include "Scorpion" probes, TaqMan, and molecular beacons. The system allows for nested and hemi-nested PCR enabling more sensitive assays. They have developed quantitative viral load assays that are

competitive in sensitivity and quantitation with Abbott and Roche. The instrument system is capable of post amplification melts. The GeneXpert system normally has 6 optical channels. However, with software modifications and additional novel chemistry, the instrument is capable of 10 optical channel assays without hardware changes. This has been implemented in the research use only Xpert MTB/XDR assay (Xie et al., N. Engl. J. Med. 2017;377:1043-54). Analysis of post amplification melting curves can also increase multiplexing capability. Cepheid appears to have halted work on their “honeycomb” project for higher level multiplexing. They have developed rapid “Xpress” assays for Flu, Flu/RSV, and Strep A that have approximately 20-minute turnaround times.

6. Manufacturer: Cepheid / Platform: Omni

Location	Sunnyvale, CA, USA
Website	http://www.cepheid.com
Time to Market	TBD

Technology Overview
• A battery powered GeneXpert • Claim to be back-compatible with current tests • Will enable faster assays (Peltier – active cooling) • No fan

Assay Specifications	
Turnaround Time	30 min to 1.5 hours (depending on which assay)
Sample Processing	Integrated in cartridge
Sample Types	Whole blood, sputum and others
Sample Volume	0.1 - 2 mL
Multiplexing	Currently 6 targets (10 targets + melt in development)

http://www.cepheid.com

Technology overview:

The GeneXpert Omni is a prototype single-module POC platform that Cepheid is currently developing and evaluating. Unlike the GeneXpert platform, the Omni is expected to be battery operated and able to withstand significant temperature variations and environmental conditions, enabling it to be used at the POC in decentralized health facilities. It will have both active heating and cooling of amplification.

The cartridge reagents and procedures used for sample preparation, amplification, detection, and results reporting on the Omni will be identical to those on the Xpert, except that cartridges used for the Omni will have the assay-specific information required to run on the Omni carried on the near field communication (NFC) label. Cepheid has stated that they are designing the Omni for emerging markets and POC. The Omni will be designed to have all solid-state components with lowered power consumption compared to the GeneXpert as well as an integrated rechargeable battery and wireless connectivity. Active heating and cooling of amplification would enable faster turnaround time and facilitate use in high temperature settings. System dimensions of the prototype are 9.1” X 3.0” X 4.2” and weight is 2.2 lbs. According to a factsheet released by MSF, the Omni price will increase from 2,895 to 5,315 USD. There is no publicly available data on the device’s operational performance or feasibility of use in remote settings at true POC locations. The Omni was originally announced in 2015 although no official launch date has been released.

7. Manufacturer: Curetis N.V. / Platform: Unyvero

Location	Holzgerlingen, Germany
Website	http://www.curetis.com/en/products.html
Time to Market	Launched in Europe CE-IVD; with FDA in U.S.

Technology Overview
The Unyvero platform consists of three separate instruments for the comprehensive diagnostics system for severe infectious diseases in hospitalized patients. DNA isolation, purification, amplification and detection are performed on the analyzer. All reagents are contained in the cartridge.

Assay Specifications	
Turnaround Time	4-5 hours
Sample Processing	Separate system, lysator required
Sample Types	Sputum, broncho-alveolar lavage, tracheal aspirates, swabs, catheters, sonication/ synovial fluids, stool, and urine
Sample Volume	~ 1 mL
Multiplexing	> 100 targets
Analyte Types	Molecular

http://www.curetis.com/en/products.html

Company background:

Curetis N.V. (Curetis) is a publicly listed (CURE: Euronext Amsterdam and Brussels) infectious disease molecular diagnostic company headquartered in Holzgerlingen, Germany and founded by former employees of Philips in 2007. They have taken the approach of establishing partnerships with other companies for instrument development and manufacturing (Zollner Elektronik), cartridge plastics injection molding (Scholz - HTiK production), and production lines (Contexo). In 2017, Curetis formed Ares Genetics GmbH, a wholly owned subsidiary, to focus on development of novel artificial intelligence-powered next generation sequencing approaches to improve the rapid detection of antibiotic resistance in patients with microbial infections in Vienna, Austria. Curetis also acquired the real-time highly multiplex qPCR-based Unyvero A30 RQ (formerly Gyronimo) technology from Carpegen GmbH and Systec GmbH.

The Unyvero platform consists of three separate instruments and is designed as a rapid, comprehensive diagnostics system for severe infectious diseases in hospitalized patients. They have developed multiple cartridges for diseases such as pneumonia, implant and tissue infections, blood stream-related infections, intra-abdominal infections and urinary tract infections with results produced in 4-5 hours. These five cartridges have all been CE-IVD marked. The system is suitable for large and medium size laboratories. Curetis has tackled high impact disease indications that have matching high clinical trial and regulatory risks and hurdles. They have also taken the high risk/value approach of developing assays that use multiple different sample types for the same assay. In April of 2018, the U.S. Food and Drug Administration granted the de novo request for its Unyvero Platform and the Unyvero Lower Respiratory Tract Cartridge, similar to its CE-IVD pneumonia assay. The Unyvero LRT cartridge is available in the USA via Curetis, USA Inc., a San Diego based subsidiary.

Technology overview:

The Unyvero System consists of three instruments: the Unyvero L4 Lysator for specimen processing, the Unyvero A50 Analyzer (for amplification and reading), and the Unyvero C8 Cockpit controller. The Curetis cartridge allows for qualitative detection of over 100 analytes, including DNA and RNA assays. Sample preparation in the Lysator uses a combination of chemical, mechanical, and thermal lysis followed by DNA purification on a column. Target organisms in their CE-IVD cartridges include eubacteria, mycobacterium, and fungi. They use a universal sample preparation protocol so that a single protocol for sample preparation can be used for many different sample types including difficult matrices such as sputum, broncho-alveolar lavage (BAL), tracheal aspirates, swabs, catheters, sonication / synovial fluids, stool, positive blood cultures, and urine. The Lysator performs the sample lysis of up to four samples in parallel. Amplification and detection takes place in the same cartridge once inserted into the Unyvero A50 Analyzer. The master mix tube needs to be inserted into the cartridge after sample processing is completed and before the cartridge is placed in the Analyzer. Amplification is by multiplex endpoint PCR followed by amplicon detection by hybridization on a low-density array by optical readout of the fluorescently-labeled PCR amplicons. The pneumonia application involves eight parallel multiplex endpoint PCRs. The Analyzer module is capable of processing two cartridges independently with full random access. For higher throughput, the user can stack up to 8 Analyzers allowing for up to 16 cartridges to be processed simultaneously.

The CE-IVD Unyvero pneumonia is for the diagnosis of community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia with multiple sample types (sputa, respiratory aspirates and bronchial lavages); this test includes 20 pathogens and 19 resistance markers. The blood culture cartridge is unique in that it tests for both Gram-positive and gram-negative organisms together – 34 organisms (plus universal bacterial target) and 16 AMR genes for a total of 103 diagnostic targets. The intra-abdominal infection application tests for 26 organisms (plus a universal bacterial target), 22 AMR genes and 2 toxin genes for a total of 130 diagnostic targets. The Unyvero ITI cartridge detects implant and tissue infections, including a total of 102 diagnostic targets: 85 microorganisms and 17 AMR markers for a total of 102 diagnostic targets.

8. Manufacturer: QIAGEN / Platform: QIAstat-Dx

Location	Barcelona, Spain
Website	https://www.stat-dx.com/
Time to Market	First CE-IVD Jan 2018 for the platform

Technology Overview
Fully integrated sample to result platform with assay cartridges. 8 real-time PCR reaction chambers with 6-plex capability for a total of 48 targets. Two products (GI and respiratory panels) are CE IVD marked. Immunoassay capability of the system as well (in development).

Assay Specifications	
Turnaround Time	~1 hour
Sample Processing	Integrated on cartridge
Sample Types	Swabs, plasma
Sample Volume	1.5 mL
Multiplexing	48 targets
Analyte Types	Molecular and immunoassay targets

Company background:

STAT-Dx is a mid-size molecular diagnostics company, located in Barcelona, Spain. They specialize in molecular diagnostic systems aimed at supporting timely and efficient patient care, while optimizing laboratory and hospital processes and operations. They are ISO 13485 certified. In late January 2018, QIAGEN (QGEN: NYSE), a public Netherlands-based life science and diagnostic company, announced it had entered an agreement to acquire STAT-Dx, developers of an integrated molecular platform – the DiagCORE® system – capable of real-time PCR for up to 48 molecular targets. With the acquisition by QIAGEN, the DiagCORE system will be branded QIAstat-Dx.

The DiagCORE system received its first CE-IVD marking in January 2018, with plans to launch the system with two CE-IVD molecular tests in Europe later in 2018, one with respiratory and the other with gastrointestinal panels. QIAGEN began launching QIAstat-Dx in Europe in April 2018 and expected to have launched QIAstat-Dx in most countries worldwide by the first half of 2019, including in the United States, following regulatory clearances.

QIAGEN expects to further enhance physicians' ability to address their patients' pressing health needs with a comprehensive menu of assays, including blood culture ID (BCID), meningitis, and pneumonia panels. QIAGEN continues to evaluate other disease states where such a flexible, high-plex platform would be able to make the highest clinical impact.

Technology overview:

The system is a fully integrated, quantitative real-time PCR for a variety of sample types and up to 48 targets. The system employs a single use assay cartridge that contains all the required sample reagents and ability to process samples on card, requiring < 1 min of hands on time for the user. QIAGEN claims that the cartridge can accept several sample types including tissue samples, liquid samples, swabs and sputum. It has modular capability and can be expanded from one to eight modules for higher throughput. Immunoassays would be run using separate, completely different cassettes employing time-resolved fluorescence that allow for this.

9. Manufacturer: Quidel Corporation / Platform: Savanna

Location	San Diego, CA, USA
Website	https://www.quidel.com/
Time to market	Launch forecasted for 2020

Technology Overview
Savanna technology can perform either traditional PCR or isothermal helicase dependent amplification in a fully integrated system. The system has been designed for use in decentralized in developed and developing country settings with an initial focus on infectious disease panels for developed countries

Assay Specifications	
Turnaround Time	< 40 minutes
Sample Processing	Integrated
Sample Types	Direct swab and processed liquid samples
Sample Volume	Unknown
Multiplexing	Up to 12 targets
Analyte Types	Molecular

Company background:
Quidel is a publicly-traded company (QDEL:NASDAQ) in San Diego, CA, USA that develops and markets multiple immunoassay and nucleic acid diagnostic platforms and tests. In addition to immunoassay platforms (Sofia and Sofia 2), they market a multiplex isothermal NAT platform for low volume and simple matrix specimens (Amplivue), moderate throughput (Solana) and higher throughput assays designed to run on both the Thermo Fisher 7500 Fast Dx Real-Time PCR Instrument and the QuantStudio Dx Real-Time PCR Instrument. Quidel recently acquired Alere's POC Triage® product line (cardiac markers and toxicology).

Technology overview:
The Savanna platform was originally developed as part of a collaboration with Northwestern Global Health Foundation. Quidel has taken sole control of the program and moved all development efforts to Quidel.
There have been significant design changes to the platform since its original inception. The instrument is smaller and more compact, including improvements in the technology. The system's minimal configuration is a single bench top instrument with one bay that can be expanded with the addition of modular bays. According to Quidel statements, Savanna will be a cartridge-based, sample-to-answer system that can run both real-time PCR and isothermal amplification assays. Savanna will be designed to provide qualitative and quantitative results and multiplex up to 12 targets, a significant advance from the original design, which could only multiplex five targets.

Quidel has worked on the instrument performance for both developed and developing countries. The initial focus will be on infectious disease panels for developed countries followed by viral assays, including fingerstick HIV viral load. Anticipated "launch" is 2020. Quidel has mentioned the first panels to be respiratory viruses, pharyngitis bacterial targets, lesion pathogens and STI bacteria targets. Room temperature reagent storage and minimal calibration and maintenance are planned. According to the company, sample preparation will require limited user interaction depending on the assay.

10. Manufacturer: Roche Molecular Systems / Platform: cobas® Liat® PCR System

Platform: cobas® Liat® PCR System
Manufacturer: Roche

Location	Pleasanton, CA, USA
Website	https://usdiagnostics.roche.com/en/point-of-care-testing/poc-testing/infectious-disease/cobas-liat-pcr-system.html
Time to Market	FDA cleared & CLIA-waived for most assays

Technology Overview
Each cobas Liat assay tube contains a set of chemical reagents used in the detection of DNA or RNA sequences unique to a particular infectious disease to enable real-time PCR at the point of care. Influenza A/B & RSV, Influenza A/B, Group A Strep are all CLIA waived. The C. diff test is CE-IVD and FDA cleared, but is moderately complex in the US.

Assay Specifications	
Turnaround Time	<20 minutes
Sample Processing	Integrated
Sample Types	Swab-based samples (nasopharyngeal, throat and stool)
Sample Volume	0.2 mL
Multiplexing	Up to 5 targets
Analyte Types	Molecular

Company background:

Roche Molecular Systems (RMS), located in Pleasanton, California, USA is a division of Roche Diagnostics, a subsidiary of the privately held Swiss multinational healthcare company, F. Hoffmann-La Roche AG. Roche has been a global pioneer and leader in molecular diagnostics since the purchase of the PCR rights and business from Cetus in 1991. Roche has multiple central laboratory Nucleic Acid Amplification test (NAAT) systems with many infectious disease assays. In this report, we are only evaluating the cobas® Liat® PCR System (Liat). This is Roche's POC entry in NAAT, a lab in a tube. Roche acquired IQuum and the Liat System in 2014 to add the missing point-of-care piece to their molecular diagnostics portfolio. FDA-cleared and CE-IVD assays for this platform include Strep A, Influenza A/B, Influenza A/B & RSV, and *C. difficile*.

Technology overview:

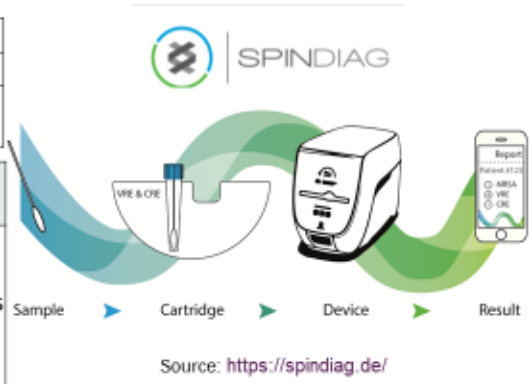
The Liat uses silica magnetic particle-based nucleic acid extraction and TaqMan probe-based real-time PCR amplification and detection. It is an integrated sample-to-answer platform. Turnaround time for assays is fast, 15-20 minutes depending on the assay. The Liat Analyzer achieves this speed primarily through a process called flow cycling. Pressure and heat are applied to disposable, flexible "tube" segments in the Liat Analyzer, mixing the specimen with reagents. Other aspects of the Liat that make it suitable for POC use include: no requirements for an external computer, equipped with network and other built-in connectivity ports, weighs just over 8 pounds, and its base is approximately 4 inches by 8 inches. In its current configuration, it runs on AC power but the instrument itself uses DC so it would be possible to run on battery power, if re-designed. Both PCR and reverse transcriptase PCR assays can be run on the platform using either real-time or endpoint detection methods. Before being purchased by RMS, IQuum had demonstrated the capability of the platform to perform a prototype HIV viral load assay. RMS has not publicly stated the Liat's multiplexing limits. It is likely that there would be constraints for large specimen volumes and difficult matrices. RMS has focused on low sample volume and lower complexity samples to date.

11. Manufacturer: SpinDiag / Platform: LabDisk

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, 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 completed development of their first product at the end of 2018, are in clinical validation in 2019 and are planning CE-IVD validation and product launch in 2020. 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

5.1 Comparison of selected top molecular platforms relevant to the MSF program

MSF is examining the feasibility of developing a novel diagnostic system and assays capable of simultaneous detection of multiple pathogens and multiple analyte types (MAPDx). The objective is to improve the ability of MSF clinicians to diagnose and manage patients presenting with severe febrile illness of unknown origin. 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 multiple platforms, and advance diagnostic capabilities in LRS. Given that MSF's priority analyte types are nucleic acids and immunoassay targets, we evaluated 107 molecular platform technologies. Of these, 22 platforms were identified that made a claim for immunoassay capabilities, yet only two of these had performance data in the public domain to support this claim.

Many factors are critical to compare when considering molecular platforms that might be of interest to the MSF program. These include platforms that have integrated sample processing for whole blood specimens from a large enough sample volume to provide sensitive results. Additional platform features that are desirable for use in LRS include battery power capability, small size, and ability to operate over a wide range of temperatures. Based on these factors, we selected 11 platforms of relevance for the MSF program. The tables below summarize key characteristics of importance to the MAPDx program and are listed alphabetically by manufacturer.

Table 2: Summary of top 11 molecular technologies with key attributes to the MAPDx program

Manufacturer	Platform	Platform capabilities (Y – yes, M – some design features, N – no)				
		Design for RLS*	**System Integration****	**Multiplexing** (NAT targets)	**Ability to accept whole blood** (P - products available, C - system design is capable though no products available, N = no capability)	**Sample Volume** (≥ 1.5mL, <1.5mL to >0.5mL, ≤ 0.5mL)
Abbott	m-PIMA Analyzer	Y	Y	>100	P	≤ 0.5mL
binx health	binx health *io*™ multi-test system	M	Y	24	N	≤ 0.5mL
bioMérieux	BioFire FilmArray	Y	M	<100	P	≤ 0.5mL
BLINK AG	BLINK One	Y	Y	unknown, high	C	≥ 1.5mL
Cepheid	GeneXpert	M	Y	6 to 10	P	≥ 1.5mL
Cepheid	Omni	Y	Y	6 to 10	C	≥ 1.5mL
Curetis N.V.	Unyvero	N	Y	>100	C	<1.5mL to >0.5mL
QIAGEN	QIAstat-Dx	M	Y	48	C	<1.5mL to >0.5mL
Quidel Corporation	Savanna	Y	Y	12	N	unknown
Roche Molecular Systems	cobas® Liat® PCR System	M	Y	5	N	≤ 0.5mL
SpinDiag	LabDisk	Y	Y	~20	N	<1.5mL to >0.5mL

*This category combines many factors including system size, operating temperature requirements, and mains vs battery power capabilities

**System ability to perform sample to result testing with integrated sample preparation

Table 3: Summary of top 11 molecular technologies and their other analyte detection capability

Manufacturer	Platform	Other analyte detection capability (P - products available, C - system design is capable though no products available, N = no capability)			Est. Time to Launch
		Immunoassay	Clinical Chemistry	Cytometry	
Abbott	m-PIMA Analyzer	N	N	N	Launched
binx health	binx health *io*™ multi-test system	N	N	N	Launched
bioMérieux	BioFire FilmArray	N	N	N	Launched
BLINK AG	BLINK One	C	N	C	3-5 years
Cepheid	GeneXpert	N	N	N	Launched
Cepheid	Omni	N	N	N	< 3 years
Curetis N.V.	Unyvero	N	N	N	Launched
QIAGEN	QIAstat-Dx	C	N	N	Launched
Quidel Corporation	Savanna	N	N	N	< 3 years
Roche Molecular Systems	cobas® Liat® PCR System	N	N	N	Launched
SpinDiag	LabDisk	C	N	N	< 3 years

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 Q2 2019 and in some instances, updated figures were provided.

7. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

One of the authors (PD) has worked previously for and owned stock in Chiron Diagnostics (now Siemens, 1990-2002), Roche Molecular Systems (2002-2005), and Cepheid (2005-2011).

One of the authors (PD) has personal relationships with employees or consultants of the following companies: Diassess (former students), Cepheid, Roche Molecular Systems, GenMark, DNAe, iCubate, and Gene POC. One of the authors (PD) has previously (2012-2013) worked indirectly as a consultant for Luminex and BioCartis through Halteres Associates.

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 diagnostic tests.

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 definition for each

[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

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.

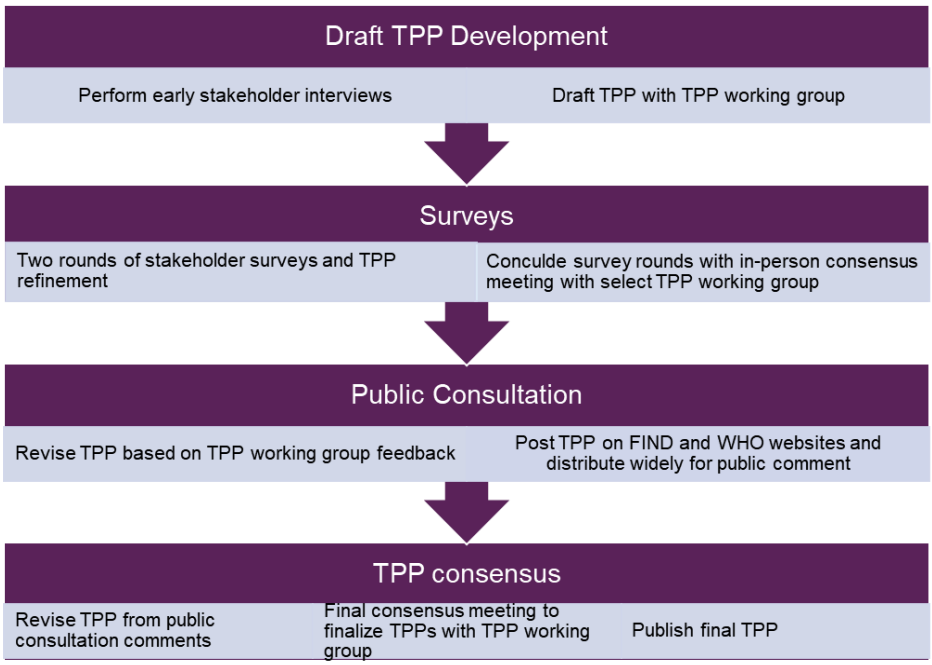


Figure 2: Overview of the TPP development process

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 diagnostics platform (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
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)

[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
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 • 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	Same as minimal, plus: • 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

[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
		• Ability to update connectivity software stack via USB or LAN	
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 time, from a single specimen, in one or more assay cartridges	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 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

[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.

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

	Characteristic	Minimum requirement	Optimal requirement
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
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

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

	Characteristic	Minimum requirement	Optimal requirement
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 – Complete list of technologies evaluated

Note: This table was developed during the initial landscape Q3 2017 through Q1 2018 and has not been updated to reflect any updates outside of the 11 technologies detailed in this report.

	Manufacturer	Platform
1	Abacus Diagnostica	GenomEra¨ CDX
2	Abbott (Alere)	m-PIMA Analyzer
3	Abbott (Alere)	Alere i
4	Abbott (IBIS)	N/A
5	Access Bio, Inc.	N/A
6	Ahram Biosystems, Inc.	Palm PCR
7	Akers Biosciences, Inc.	minDNA™
8	Akonni Biosystems, Inc.	TruDx3000
9	Amplino	TBD
10	Analytik Jena AG	N/A
11	Aquila Diagnostic Systems Inc.	Accutas
12	Atonomics A/S	Trace
13	Axela (Angle Biosciences)	Ziplex¨ System
14	Axxin	T-8 and T-16 Iso
15	baebies	Finder
16	BD Diagnostics	BD Max
17	binx healthcare	binx health *io*™ multi-test system
18	Biocartis SA	Idylla™
19	BioCeryx	N/A
20	bioMérieux (BioFire Diagnostics)	BioFire
21	Bioneer	AllinOneCycler
22	BLINK AG	Blink One
23	BluSense Diagnostics	BluBox
24	Canon U.S. Life Sciences	N/A
25	ChipCare	Polyvalent Analyzer (PAx) platform
26	Click Diagnostics	N/A
27	Coris BioConcept	Trapist V6
28	Coyote Biosciences	Mini8Plus
29	Curetis AG	Unyvero
30	Danaher (Cepheid)	GeneXpert/GeneXpert Xpress
31	Danaher (Cepheid)	Omni
32	DestiNA Genomics Ltd.	N/A
33	Diagnostics for All (DFA)	DFA NAAT (non-instrumented)
34	Diagnostics for the Real World	SAMBA II
35	DiaSorin S.p.A. (Focus Diagnostics)	Integrated Cycler
36	Diassess	N/A
37	DNA Electronics Ltd. (DNAe)	LiDia
38	DxNA, LLC	GeneSTAT
39	Eiken Chemical Co., Ltd.	LA-500 and LF-160
40	Enigma Diagnostics Limited	MiniLab

41	ERBA Molecular (Lumora Ltd)	Sells sample prep instrument and assays
42	Espira, Inc.	Automated Pathogen Detection Uni
43	ExcitePCR (PositiveID Corporation)	FireflyDx
44	Genedrive (was Epistem)	Genedrive
45	GenePOC Inc.	Revogene
46	GeneReach	POCKIT[a] Micro Series Nucleic Acid Analyzer
47	Genmark	Eplex System
48	Genomica	NeDXa
49	Great Basin Corporation	Great Basin Analyzer
50	Hai Kang Life Corporation Limited	EFADchip[¨]
51	Hain Lifescience GmbH	Multiple. No integrated molecular platform
52	HiberGene Diagnostics Ltd	HG Swift
53	iCubate, Inc.	iCubate
54	Immunexpress Group	N/A
55	InSilixa	HYDRA-1K
56	InstantLabs	Lab in a Box
57	Instrumentation Laboratory	N/A
58	INT (integratednano)	Palladium System
59	LexaGene	LX2™ Genetic Analyzer
60	LiquiLume Diagnostics, Inc.	N/A
61	Luminex (Aries)	Aries
62	Luminex (Nanosphere)	VERIGENE[¨] NANOGRID
63	Magnomics	N/A
64	Mast Group Ltd.	N/A
65	MBio Diagnostics, Inc.	LightDeck Technology
66	Meridian Bioscience, Inc.	illumigene
67	Mesa Biotech	Mesa Biotech Dock
68	Mesa Tech International, Inc.	N/A
69	Metaara Medical Technologies Inc.	N/A
70	Micronics Inc. (A Sony Group Company)	PanNAT[¨] Molecular Diagnostic System
71	Molbio Diagnostics Pvt. Ltd.	Truelab[a] Real Time quantitative micro PCR system
72	MP Biomedicals, LLC	N/A
73	MycroLab Diagnostics Pty Ltd.	N/A
74	Nanobiosym (Nanobiosim Diagnostics)	Gene-RADAR®
75	NanoBioSys Inc.	UtlraFast LabChip Real-time PCR G2-3
76	NanoDetection Technology	N/A
77	NanoIVD, Inc.	NanoIVD Clinical Analyzer I
78	Nanomix, Inc	eLab System
79	NetBio, Inc. (Ande)	ANDE[a] Rapid DNA System
80	NVS Technologies	N/A
81	Opko Diagnostics (Opko Health)	Claros 1
82	OptiGene Ltd.	Genie[¨] III

83	Optolane	N/A
84	Panagene	N/A
85	Paratus Diagnostics	PreparedNow® System
86	Pinpoint Science Inc.	N/A
87	Pretect (formerly NorChip)	N/A
88	PuckDx	Desktop biology platform
89	QIAGEN N.V	Rotor-Gene Q MDx, QIAsymphony RGQ MDx
90	QIAGEN (STAT-DX)	QIAstat-Dx
91	QuantuMDx Group	Q-POC
92	Quidel Corporation	Savanna / Wildcat
93	Rheonix Inc.	Encompass MDx¨ workstation
94	Roche Molecular Systems	cobas® Liat® PCR System
95	SA Scientific	N/A
96	Seegene, Inc.	N/A
97	SlipChip (now Talis Biomedical Corp.)	N/A
98	Spartan Bioscience Inc.	Spartan Cube
99	SpinDiag	LabDisk
100	T2 Biosystems, Inc	T2MR
101	Thermal Gradient, Inc.	FLASHDIRECT
102	Thermo Fisher Scientific (Life Technologies Corporation)	QuantStudio platforms
103	Two Pore Guys	N/A
104	Ustar Biotechnologies (Hangzhou) Ltd.	Easy NAT
105	Veredus Laboratories Pte Ltd	VerePLEXª Biosystem
106	Wave 80 Biosciences	N/A
107	Xagenic Inc.	X1 Platform

N/A: “No instrument platform” or TBD (to be determined)