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 diagnostic platform (MAPDx). 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 the 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 these 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 empower the testing facility to cover multiple diagnostic needs while investing in fewer instruments.

Developing a Target Product Profile

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

[2] Crump J a, 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

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 the end user's needs for a defined use case. TPPs often include an optimal and minimal 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. To develop a draft TPP for this diagnostic platform, key opinion leaders 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.

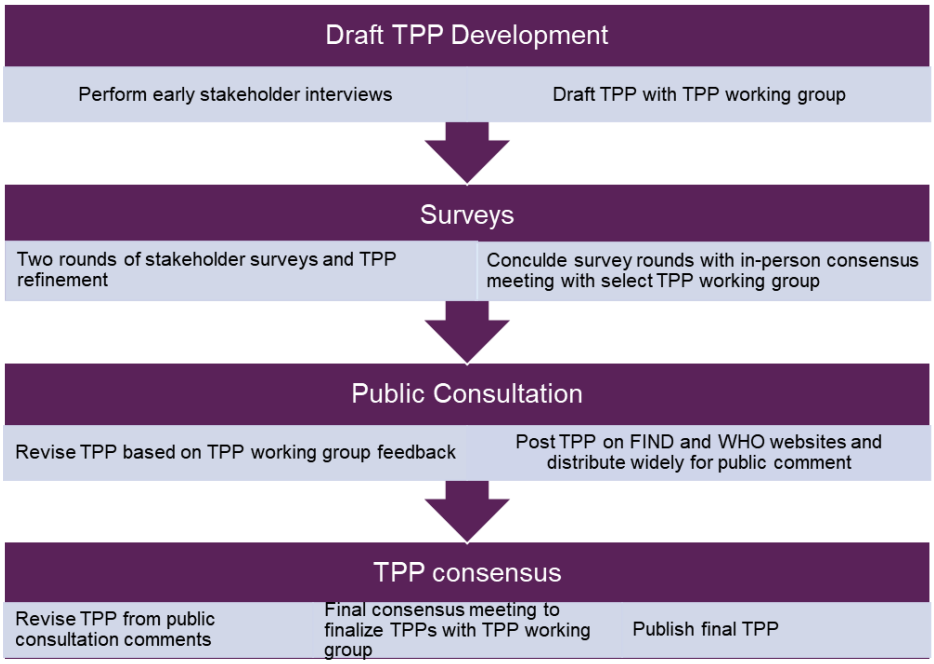

Figure 1: Overview of TPP Development Process

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 (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 for 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 wifi 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	Same as minimal, plus: • Multi-band GSM chipset 2G, 3G, LTE • Integrated Bluetooth 5.0 • Integrated wifi 802.11ac • Bi-directional communication – ability to update connectivity software stack
18	**Data Export**	Export of all instrument and test data over integrated hardware.	Same as minimal, plus scheduled/automatic data export using

[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
		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.	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
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

[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
			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 0–50°C. 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 0–50°C. 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

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

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