Target Product Profile for a Multiplex Multi-Analyte Febrile Illness Test for use on the MAPDx platform

	Characteristic	Minimum Requirement	Optimal Requirement
		Scope of the Platform	
1	**Intended Use**	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[1] to test for the pressence of markers of current infection by target pathogens	
2	**Description of System**	The system will consist of an instrument[2] designed for use in combination with a self-contained, disposable assay cartridge(s)[3] containing all required reagents to execute a test from sample to result	
3	**Target Use Setting**	Level 2[4] 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[4] 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 certificates)	Minimally skilled healthcare personnel (e.g. 3-6 months, able to operate an integrated test with minimal additional steps)
5	**Target population**	Adults to children > 6 months of age	Same, plus neonates (including prematures) up to 6 months of age
	Instrument		
6	**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	
7	**Size**	Small, table-top instrument (50 cm x 75 cm by 50 cm, or smaller))	
8	**Weight**	≤ 25 kg	≤ 10 kg

[1] 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."

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

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

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

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9	**Power Requirements**	Local 110-220 AC mains power, plus UPS (to complete current cycle); UPS and circuit protector must be integrated within the system	Same, with rechargeable battery back-up (8-hour operation)
10	**Throughput**	Random access[5] required[6]with throughput up to 8 sample runs per instrument per 8-hour day	Random access required[6] with throughput up to 40 sample runs per instrument per 8-hour day
11	**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
12	**Biosafety**	Closed, self-contained system; easy decontamination of instrument surfaces	
13	**Training**	<2-days training for skilled laboratory staff	<1-day training for minimally skilled staff
14	**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; and 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
15	**Patient Identification Capability**	Manual entry of alphanumeric patient identifier keypad or touch screen compatible with protective gloves	Same, plus bar code, RFID or other reader
16	**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	
17	**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.)	

[5] 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

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

	Characteristic	Minimum Requirement	Optimal Requirement
18	**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; Ability to update connectivity software stack via USB or LAN Global position	Integrated Local Area Network (LAN) port; Multi-band GSM chipset 2G, 3G, LTE; Integrated Bluetooth 5.0; Integrated WI-FI 802.11ac; USB 3.0; Internally designatable static IP address; Support for DHCP issued IP addresses; Bi-Directional communication – ability to update connectivity software stack
19	**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; and Connectivity to external printer	Export of all instrument and test data over integrated hardware; Export of data via GSMA SMS; Secured data export with end-to-end encryption; Data export using interoperable standards Configurable destination IP and DNS address; User initiated data export; and Scheduled/automatic data export Connectivity to external printer
20	**Manufacturing**	ISO 13485:2016 compliant	
21	**List Price[7] of Instrument**	≤ $15,000 USD	≤ $5,000 USD
	Assay Cartridge		
22	**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'[8] design specifications made available by the manufacturer of the multiplex diagnostic platform to selected assay developers worldwide for use on such platform	

[7] 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.

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

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

	Characteristic	Minimum Requirement	Optimal Requirement
23	**Pathogen Targets**	Detection of all the following to the limit of detection listed in Appendix 1: • Typhoidal salmonella • Streptococcus pneumoniae • Staphylococcus aureus • Non-typhoidal salmonella • Escherichia coli • Rickettsial spp • Leptospira spp • Brucella spp • Burkholderia pseudomallei • Coxiella burnetii	Same, plus detection of any of the following to the limit of detection listed in Appendix 1 in descending level of priority: • Neisseria meningitidis • Klebsiella spp • Orientia tsutsugamushi • Haemophilus influenzae • Dengue virus (all serotypes) • Lassa virus • Histoplasma capsulatum • Enterococcus faecalis • Borrelia recurrentis • Chikungunya virus • Pseudomonas spp • Acinetobacter baumannii • Enterobacter spp
	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; Analytes per pathogen target are listed in Appendix 1	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); Analytes per pathogen target are listed in Appendix 1
24	**Clinical Sensitivity**	≥ 90% (95% CI) per pathogen based upon optimal sample volume input	≥ 95% (95% CI) per pathogen based upon optimal sample volume input
25	**Clinical Specificity**	≥ 95% per pathogen based upon optimal sample volume input	≥ 98% per pathogen based upon optimal sample volume input
26	**Multiplexing Capabilities**	Ability to detect a minimum of 6 pathogens[9] 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
27	**Limit of Detection in Multiplex Format**	Equivalent or improved relative to reference assays for similar target analytes (see Appendix 1 below)	
28	**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	
29	**Additional Third-Party Consumables**	None, except for sample collection and sample prep (e.g. volumetric pipettes)	None; cartridges contain all required reagents
30	**Specimen Type**	Whole blood	

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

	Characteristic	Minimum Requirement	Optimal Requirement
31	**Sample Volume**	The minimal sample volume required to reach clinically relevant sensitivities in a 24-hour period, which in some cases could require up to 10 mL depending on sample volume and limit of detection (See Appendix 2);[10] For children 5 years to 6 months of age should require no more than 5 mLs of whole blood	Same as minimal requirements and for neonates (including prematures) -or children <2kg should require no more than 2 mL of whole blood
32	**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 precisions steps required to be performed by the user
31	**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. *Staphylococcal epidermidis*)	
32	**Interfering Substances**	No interference for an individual or mixtures of analytes due to interfering substances	
33	**Test Result**	Quantitative based on the analytes of detection; Qualitative result available to user where that result is sufficient to inform clinical decision making	
34	**Time to Result**	<90 minutes	<30 minutes
35	**Controls – Internal Process**	A full internal process control must be integrated into the assay cartridge and the instrument	
36	**Controls – Positive/Negative**	External positive and negative controls are not required for each test and but are performed daily	External positive and negative controls are not required for each test and do not need to be run daily
37	**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
38	**Environmental Stability – Operating Range**	10 – 35°C	5 – 45°C
39	**Waste/Disposal Requirements**	Direct disposal or incineration of consumables	Same, and no use of cyanide-containing reagents

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

	Characteristic	Minimum Requirement	Optimal Requirement
40	**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
41	**Manufacturing**	ISO 13485:2016 compliant	
42	**List Price[7] of Assay Cartridge**	≤ $15 USD at volume production	≤ $5 USD at volume production

Appendix 1: List of Reference Testing and Limit of Detection for Priority Pathogens

Rank	Pathogen	Sample type	Gold standard	Pathogen circulation/mL (Ref)	**Analyte Type Required** Molecular and/or serology (antibodies, antigens and host biomarkers)
1	Typhoidal salmonella	WB	Blood culture	1 (Wain, 1998; S. typhi)	Molecular
2	Streptococcus pneumoniae	WB	Blood culture	1-30 (Lehman 2008)	Molecular
3	Staphylococcus aureus	WB	Blood culture	1-30 (Lehman 2008)	Molecular
4	Non-typhoidal salmonella	WB	Blood culture	1 (Wain, 1998; S. typhi)	Molecular
5	Escherichia coli	WB	Blood culture	200 (Yagupsky, 1990)	Molecular
6	Rickettsia ssp	Buffy coat / WB	IFA (4-fold rise)/qPCR	210 (Dittrich, 2014)	Molecular & Serology
7	Leptospira	WB/serum	MAT (4-fold rise)/qPCR	10000 (Agampodi,2012)	Molecular & Serology
8	Brucella	WB/serum	Blood culture/serology	88 (Young, 1995)	Molecular & Serology
9	Burkholderia pseudomallei	WB/pus	Blood culture	~10 (Supaprom et al. 2007)	Molecular
10	Coxiella burnetii	WB/serum	IFA (4-fold rise)/qPCR	10 (Wielders, 20103)	Molecular & Serology

11	Neisseria meningitidis	WB	Blood culture	$1.6x10^6$ (DNA copies/mL; children) (Hackett et al. 2004 10^4 CFU/mL (Zwahlen et al. 1984)	Molecular
12	Klebsiella	WB	Blood culture	10 (Yagupsky, 1990)	Molecular
13	Orientia tsutsugamushi	Buffy coat / WB	IFA (4-fold rise)/qPCR	300-10^6 (Singhsilarak et al. 2005; Dittrich et al. 2011)	Molecular & Serology
14	Haemophilus influenzae	WB/CSF	Culture	NA	Molecular
15	Dengue virus (all serotypes)	WB/serum	IFA, ELISA (4-fold rise)/qPCR, NS1	100000 (Alm, 2014)	Molecular & Serology
16	Histoplasma capsulatum	WB/urine	Blood culture/Antigen		Molecular
17	Lassa virus	WB/serum	qPCR	600 (Trombley, 2010)	Molecular
18	Enterococcus faecalis	WB	Blood culture	1-30 (Lehman 2008)	Molecular
19	Borrelia recurrentis	WB	Microscopy	10^3-10^5 (Fotso and Drancourt, 2015)	Molecular
20	Chikungunya virus	WB	PCR	10^4 (Reddy et al. 2014)	Molecular & Serology
21	Pseudomonas	WB	Culture	NA	Molecular
22	Acinetobacter baumannii	WB	Blood culture	NA	Molecular
23	Enterobacter spp	WB	Blood culture	NA	Molecular

Appendix 2: Pathogen load per blood volume

Required test blood volumes will be influenced by the lower limit of detection (LOD) of the test (e.g., and LOD would require 10 mL to detect Typhoidal salmonella)

Rank	Pathogen	Pathogen circulation/mL (Ref)	Number of pathogens per 1 mL	Number of pathogens per 5 mL	Number of pathogens per 10 mL
1	Typhoidal salmonella	1 (Wain, 1998; Wain et al. 2001; S. typhi)	1*	5	10
2	Streptococcus pneumoniae	1-30 (Lehman 2008)	1*	5	10
3	Staphylococcus aureus	1-30 (Lehman 2008)	1*	5	10
4	Non-typhoidal salmonella	1 (Wain, 1998; S. typhi)	1*	5	10
5	Escherichia coli	200 (Yagupsky, 1990)	200	1000	2000
6	Rickettsia ssp	210 DNA copies/mL (Dittrich, 2014)	210	1050	2100
7	Leptospira	10000 (Agampodi,2012)	10000	50000	100000
8	Brucella	88 (Young, 1995)	88	440	880
9	Burkholderia pseudomallei	~10 (Supaprom et al. 2007)	1*	5	10
10	Coxiella burnetii	10 (Wielders, 20103)	10	50	100
11	Neisseria meningitidis	$1.6x10^6$ (DNA copies/mL; children) (Hackett et al. 2004 10^4 CFU/mL (Zwahlen et al. 1984)	10000	50000	100000

12	Klebsiella	10 (Yagupsky, 1990)	10	50	100
13	Orientia tsutsugamushi	300-10^6 (Singhsilarak et al. 2005; Dittrich et al. 2011)	106	$5x10^6$	10^7
14	Haemophilus influenzae	NA	NA	NA	NA
15	Dengue virus (all serotypes)	100000 (Alm, 2014)	100000	500000	1000000
16	Histoplasma capsulatum	NA	NA	NA	NA
17	Lassa virus	600 (Trombley, 2010)	600	3000	6000
18	Enterococcus faecalis	1-30 (Lehman 2008)	1*	5	10
19	Borrelia recurrentis	10^3-10^5 (Fotso and Drancourt, 2015)	1000	5000	10000
20	Chikungunya virus	10^4 (Reddy et al. 2014)	10,000	50,000	100,000
21	Pseudomonas	NA	NA	NA	NA
22	Acinetobacter baumannii	NA	NA	NA	NA
23	Enterobacter spp	NA	NA	NA	NA

*Targets with 1 circulating pathogen per mL are statistically unlikely to be present in each 1mL, therefore > than 1mL would be required to ensure pathogens are present for detection; NA: not available