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WHO R&D Blueprint: Priority Diagnostics for CCHF

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Abstract

Documentation and coordination for diagnostic Target Product Profiles for CCHF as part of selected WHO R&D Blueprint and Roadmaps priority diseases in compliance with the WHO harmonized methodology

World Health Organization

This WHO TPP document should inform product developers, regulatory agencies, procurement agencies and funders on R&D and public health priorities, and is intended to facilitate the most expeditious development of products that address the greatest and most urgent public health need.

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Abbreviations

Ag	Antigen
BSL	Biosafety level
CCHF	Crimean-Congo haemorrhagic fever
CCHFV	Crimean-Congo haemorrhagic fever virus
CE	CE marking, Conformité Européene
CLIA	Chemiluminescence assay
CO, S/CO	Cutoff, Sample vs. cutoff signal
ECL	Electrochemiluminescence immunoassay
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
FDA	US FDA, Food and Drug Administration
IFA	Immunofluorescence assay
IgG	Immunoglobulin G (late immune response)
IgM	Immunoglobulin M (early immune response)
IU	International units
LAT	Latex agglutination test
LFA	Lateral flow assay (see RDT)
LMIC	Lower to middle income country
LOD	Limit of detection
LOQ	Limit of quantitation
mL	Milliliter
NAT	Nucleic acid test, also Nucleic acid amplification test
NPT	Near-patient (test used in a peripheral laboratory setting)
POC	Point of care (test used outside of a laboratory setting)
RDT	Rapid diagnostic test (lateral flow assay POC test)
RNA	Ribonucleic acid (viral nucleic acid)
RUO	Research use only
RT-PCR	Reverse transcriptase polymerase chain reaction
SRA	Stringent regulatory authority
TPP	Target product profile
uL	Microliter
USD	US dollar
WB	Western blot
WHO PQ	World Health Organization Pre-Qualification

WHO R&D Blueprint: Priority Diagnostics for CCHF

Introduction

The WHO R&D Blueprint for Action to Prevent Epidemics establishes a platform for R&D preparedness that is intended to accelerate research and product development in advance of and during epidemics caused by the world's most significant infectious disease threats.[1–4] The R&D Roadmaps are intended to focus and catalyze international R&D effort to ensure the coordinated development of medical countermeasures (diagnostics, therapeutics and vaccines) thus reducing the time for new medical technologies and products to reach affected countries in a public health crisis. For diagnostics in particular, the emphasis of the R&D Roadmaps is toward acute and early detection of disease during outbreaks.

The R&D Roadmap for Crimean-Congo Haemorrhagic Fever (CCHF) is the product of broad consultation with leading experts from CCHF-affected countries, international product R&D experts and other stakeholders.[5] In 2018 and 2019, Roadmap goals and strategic priorities were defined and updated for developing improved diagnostics, therapeutics, and vaccines for CCHF.[6,7] Part of the overarching vision for the CCHF Roadmap is 'to be able to reduce death and morbidity from CCHF through safe and affordable effective treatments informed by rapid, reliable, simple-to-use and easily accessible diagnostics by 2023'. The development and validation of *in vitro* diagnostic assays for CCHF is therefore a priority for the WHO R&D Roadmap to enable effective medical intervention and infection control in both centralized and decentralized settings.

This CCHF TPP document is intended to be a framework for facilitating the diagnostic development goals of the WHO R&D Roadmap for CCHF, following prioritization of the diagnostic needs identified in the R&D Roadmap for acute and early case detection of CCHF. Use scenarios have been developed to define the critical functionality for testing in centralized reference laboratories as well as decentralized/peripheral health center or district hospital settings.[a] These scenarios serve as a bridge to the target product profile (TPP), a detailed technical document for product development that describes the desired characteristics, features, and performance of diagnostics for a specific setting. Following expert consultation, the highest priority CCHF TPPs will be published to engage the diagnostic community for refinement and validation.

R&D Roadmap: Strategic Goals and Milestones for CCHF Diagnostics

Updated in 2019,[7] the CCHF R&D Roadmap outlines the strategic goal of 'affordable, qualified nucleic acid and serology tests accessible for use in CCHF-affected countries by 2020 followed by the development and introduction of near-patient and/or point-of-care tests by 2023. Specifically the R&D Roadmap prioritized the need for development and validation of 1) molecular diagnostics for pan-CCHFV detection

[a] Decentralized diagnostics are often described as point-of-care (POC) tests if they can be used at the bedside or community setting, or as near-patient (NPT) tests if they are intended to be used in an adjacent hospital or clinic laboratory.

for use in reference labs and near-patient settings, and 2) serology tests including ELISA and rapid diagnostic tests (RDTs). Specific diagnostic gaps were identified for quantitative viral RNA detection, lineage/clade coverage, sample type, antigen capture sensitivity, and sample collection/inactivation.

The Landmark milestones in the 2019 update include (*in chronological order*):

- By **March 2019**, define TPPs for molecular (RT-PCR) and serologic/antigen (IgM, Ag) CCHF diagnostic tests suitable for use (i) in reference laboratories and (ii) decentralised near-patient settings.
- By **2020**, through international collaboration, validation of commercial real-time RT-PCR tests (qualitative and quantitative) and serological tests using panels of well-characterised clinical samples that cover the main circulating CCHFV strains.
- By **2022**, develop and qualify one or more commercial tests suitable for near-patient diagnosis of CCHF, including evaluation in relevant healthcare settings in CCHF-affected regions to a standardised protocol.
- By **2022**, define TPPs for rapid point-of-care tests (with minimal requirements for biosafety precautions and staff training).
- By **2023**, develop and qualify commercial tests suitable for point-of-care use, including evaluation in relevant healthcare settings in CCHF-affected regions to a standardised protocol.

In summary, the CCHF R&D Roadmap Landmark milestones describe the identification, development, and validation of nucleic acid (RNA) and serologic/antigen tests (IgM, Ag) for use across reference laboratory, near-patient, and point-of-care settings. The timelines described above define the relative development priority for CCHF diagnostic TPP development:

1. CCHF RT-PCR – reference laboratory & near patient laboratory settings
2. CCHF IgM, Ag ELISA – reference laboratory & near patient laboratory settings
3. CCHF IgM, Ag RDT – lateral flow assay (LFA), point-of-care (POC) design

CCHF Diagnostic Overview

Diagnostic tests used to diagnose CCHF[8,9] include nucleic acid tests (NAT)[b] for RNA detection, serological (IgG, IgM) and antigen (Ag) capture, and virus isolation.[c] Active CCHFV infection can be detected by amplification of CCHFV RNA, or by the capture of CCHFV-specific IgM or viral antigen, or by a significant increase in CCHF-specific IgG titer following the acute phase of infection. For survivors, IgG antibodies can be detected long after acute viral infection.

NAT assays can detect active infection (CCHFV RNA) with the greatest sensitivity at the earliest time point. NAT tests can produce a qualitative or a quantitative result; a quantitative viral load test may provide

[b] For CCHF, RT-PCR is the most common type of NAT, however other nucleic acid test methods can be used.
[c] Virus isolation is rarely used because of the stringent biosafety containment (BSL-4) recommended for CCHF virus.

additional information on disease severity, effect of therapeutic interventions, and prognosis. Depending on the probe design, NAT assays can be sensitive (or insensitive) to genetic sequence.[d] A positive PCR test result indicates active CCHFV infection, however negative PCR may not rule out CCHFV infection due to variations in test sensitivity and genetic diversity of the virus.

Protein assays (ELISA, IFA, LFA) selectively capture CCHFV-specific antibodies or antigens, and are less impacted by genetic diversity, however it has been observed that severe cases of CCHFV infection may not mount a detectable antibody response. Given the observed range of CCHFV sequence diversity and immune response, it has been recommended that nucleic acid tests be used in combination with serological assays for highest clinical sensitivity,[10–12] though many low-resource settings may not have the capacity, especially at the early stages of an outbreak.[13]

Standardization. There is currently no "gold standard" or reference test for CCHF that is universally accepted. Further, there is a lack of standardization within the existing NAT and serology assays available for CCHF. Though several commercial tests are available, the majority of reference laboratories use in-house assays that were developed from regional circulating strains, providing limited diagnostic application across all clades and variants. Only a few of these tests have published data for external quality assurance (EQA) or proficiency testing. Moreover, there are no reference reagents (including International Standards) for calibrating and harmonizing assays.

Infrastructure and containment. Nucleic acid amplification is highly susceptible to contamination and typically requires laboratory infrastructure for containment (e.g. biosafety hood, clean room); several automated "self-contained" solutions have been successfully implemented for decentralized NAT testing.[14,15] ELISA tests can be run on the benchtop in a more modest laboratory environment, however a POC counterpart for ELISA-based antibody and antigen detection would be valuable. Antibody and antigen RDTs are designed for field use and are useful for rapid screening, but can fall short of the sensitivity needed for confirmation.

CCHF patient samples present an extreme biohazard risk and should only be handled under maximum biological containment conditions (BSL-3/4 where available) or unless inactivated[16,17] for processing in a more modest biosafety environment. Most peripheral laboratories have limited containment and would be better served by a minimal sample preparation protocol – preferably only specimen transfer into an enclosed cartridge or cassette, with diagnostic testing under enhanced BSL-2 conditions.[18]

Use Scenarios for High Priority CCHF Diagnostics

The CCHF R&D Roadmap recommended the development and validation of diagnostics for both reference laboratory and decentralized near-patient settings. Use scenarios help inform test design, specifically here in describing the setting for CCHF testing as it exists today: available infrastructure, skill level for test

[d] There are six (possibly seven) CCHF viral lineages/clades identified across Africa, Asia, Europe, and the Middle East. Clade I (Africa 3), Clade II (Africa 2), Clade III (Africa 1), Clade IV (Asia 1/Asia 2), Clade V (Europe 1), Clade VI (Greece), Clade VII (Iran-Kerman/22).

operation, anticipated test demand (at peak of outbreak), and timing for results. In this way, the use scenario serves as a bridge to the more detailed target product profile (TPP) characteristics for the diagnostic test features and performance.

The use scenarios below are intended for acute and early case detection during an outbreak of CCHF. Use Scenario 1 describes a typical LMIC reference laboratory; Use Scenario 2 describes a typical peripheral near-patient laboratory.[19] These scenarios are intended to highlight general features and challenges. For example, most central reference laboratories have the infrastructure for any test, however results may have a longer turnaround time due to specimen transport and batch processing. Decentralized testing can enable a more rapid intervention, however peripheral laboratories often lack the infrastructure for more complex tests. Other use scenarios can be designed for routine screening or surveillance for endemic disease (not included here).

Use Scenario 1: Reference laboratory

Use Scenario 1 describes the capacity for CCHF case detection in a reference laboratory setting, using specimens transported to the laboratory and processed in batch. Most central reference laboratories have the infrastructure for any test. Test results are generally available within 1-2 days, though sample transport and return of test results from reference laboratory to clinic often requires days to weeks.

Use Scenario 1: CCHF case detection in a reference laboratory	
Clinical Impact	Detection and confirmation of active CCHFV infection, preferably acute/early stages Quantitative result may indicate severity of infection
Use Setting	Reference laboratory (requires specimen transport) Resources typically include: biosafety hood, centrifuge, calibrated pipets, refrigerator, -20°C and -80°C freezers, network for specimen transport and storage
Target Population	Patient meeting the clinical definition of suspect CCHF, specimen transported from health care facility to reference lab
Test Demand (max)	Up to 100 specimens per day at peak outbreak (200-300 tests during convalescence[e])
Test Operator	Laboratory technician (2+ year certificate)
Test Complexity	Operators can reliably process high (≤ 5 steps) to moderate (≤ 3 steps) test complexity Capacity for manual sample preparation and processing in biosafety hood Capacity for daily/weekly external controls and calibration
Turnaround Time	Next-day test results (batch processing), may have 2 week turnaround to clinic

Use Scenario 2: Peripheral health center or district hospital

Use Scenario 2 describes the capacity for CCHF case detection at a peripheral laboratory setting, using specimens obtained within 1 hour from patients presenting to an adjacent health care facility. Peripheral

[e] If no access to RT-PCR testing (ELISA only)

laboratories typically have fewer resources and limited capacity for manual processing. Test results are can obtained within a day for rapid case management, preferably while the patient is still at the clinic.

Use Scenario 2: CCHF case detection in a near-patient laboratory	
Clinical Impact	Detection of active CCHFV infection for case management Detection of active CCHFV infection, preferably acute/early stages
Use Setting	Health care facility or near-patient hospital laboratory Resources may be limited: benchtop, microcentrifuge, transfer pipets, refrigerator
Target Population	Patient meeting the clinical definition of suspect CCHF, presenting to adjacent health care facility
Test Demand (max)	Up to 20 specimens per day at peak outbreak (up to 50 tests if multiple tests per patient)
Test Operator	Laboratory technician (1-2 year certificate); doctor, nurse, healthcare worker
Test Complexity	Operators can reliably process moderate (≤ 3 steps) to minimal (sample addition only) test complexity Little to no capacity for manual sample preparation and processing Capacity for weekly external controls
Turnaround Time	Same-day or next-day test results (can be while-you-wait test)

Target Product Profiles for CCHF Diagnostics

From the diagnostic use scenarios, target product profiles (TPPs) have been developed to provide detailed performance specifications for the tests needed for CCHF. TPP characteristics are typically described with a range for minimal to optimal performance specifications. Any diagnostic test is acceptable as long as performance falls within the range of parameters outlined in the TPP, however the preferred test is expected to meet most of the optimal performance specifications.

The TPPs presented below are designed for CCHFV test performance inclusive for near-patient laboratory and reference laboratory settings, as NPT platforms have demonstrated high performance even in low infrastructure settings.[14,15] TPP 1 is designed for a CCHFV NAT assay, TPP 2 is designed for a CCHFV ELISA assay, and TPP 3 is included for a CCHFV RDT. (Specifications for near-patient instrumentation are included as a separate TPP in Annex A.)

TPP 1: CCHF RT-PCR Assay

RT-PCR is the most common type of NAT test used for CCHF, and is used as a general descriptor for NAT testing. CCHF tests are needed that more broadly detect the circulating CCHFV clades (African clades I-III, Eurasian clades IV-VII), with appropriate clinical validation and quality assurance.

Specification	Minimal Performance	Optimal Performance
Intended Use	**Qualitative** RT-PCR test for detection of CCHFV RNA in human specimens for evidence of active CCHFV infection	**Quantitative** RT-PCR test for detection of CCHFV RNA in human specimens for evidence of active CCHFV infection

Kit Overview	Kit includes most assay components and reagents; user may supply third-party reagents (e.g. water or buffer) and consumables for sample collection and preparation	Kit includes all assay components and reagents; all materials required to test one patient are included in individually packaged, self-contained cartridge for cartridge-based platforms
Analytes	CCHFV RNA, validated for Eurasian clades IV-VII	CCHFV RNA, validated for Eurasian and African clades I-VII
Time to Result	<6 hours	<2 hours
Specimen Type	Plasma, serum, urine	Plasma, serum, urine, whole blood
Sample Input	≤ 1 mL	≤ 100 uL
Sample Preparation	Manual (conventional) sample prep for CCHFV RNA extraction and purification.	Automated or semi-automated sample prep: ≤3 manual steps.
Test Output	Qualitative: CCHFV detected/not detected above threshold	Quantitative: CCHFV IU/mL or Ct
Limit of Detection (LOD)	1000 IU/mL	100 IU/mL or Ct??
Linear Range (LOQ)	10^4 to 10^7 IU/mL	10^3 to 10^8 IU/mL or Ct15-Ct38
Clinical Sensitivity	≥95%	≥98%
Clinical Specificity	≥95%	≥98%
Cross Reactivity	No cross-reactivity with other endemic or syndromic pathogens	
Interfering Substances	No interference for individual or mixtures of analytes, endogenous/exogenous substances	
Assay Process Controls and Calibration[f]	Process may require external positive control Daily calibration for quantitative result	Internal full process control integrated into assay Weekly calibration for quantitative result
Third-Party Instrumentation	Centrifuge, calibrated pipettors, pipet tips, timer, miscellaneous lab consumables; -20C freezer, IPC sets, laboratory boxes, ventilation/negative pressure	Requires transfer pipettes only
Opened Kit Stability	2-8 °C for up to 3 hours prior to use	≤30 °C for up to 1 hour prior to use
Unopened Kit Storage and Shelf Life	-20°C (or dry ice) for transport, up to 6 months storage	No cold chain requirements for transport or storage: 12 months, 70% humidity from date of manufacture (based on stability studies) at up to 30°C
Biosafety/Disposal Requirements	Biohazard disposal as appropriate for potentially infectious material	Specimens deactivated and enclosed within cartridge; biohazard disposal (as appropriate)
Kit Certification	ISO 13485:2016 certified	ISO 13485:2016 certified; approved by stringent regulatory authority (SRA)
Price of Single Test	≤$30 USD at volume production	≤$10 USD at volume production

[f] Calibrated to international standard when available

TPP 2: CCHF ELISA Assay

ELISA tests for CCHF are typically limited to reference laboratories, as they require high biosafety containment to process CCHFV. In the case of CCHF, commercial ELISA tests are indicated for research-use only (RUO); clinically validated and quality-assured commercial tests for detection of active CCHFV infection are needed.

Specification	Minimal Performance	Optimal Performance
Intended Use	ELISA test for detection of CCHFV-specific human IgM or CCHFV Ag in human specimens for evidence of active CCHFV infection	ELISA test for detection of CCHFV-specific human IgM and CCHFV Ag in human specimens for evidence of active CCHFV infection
Kit Overview	Kit includes most assay components and reagents for 96-well plate or 12x8 strip format. User may supply some reagents (e.g. water or buffer) and some consumables for sample collection and preparation; 96-well plates or 12x8 strips are pre-coated with capture Ag/Ab	Kit includes all assay components and reagents. All materials required to test one patient are included in individually packaged, self-contained cartridge; 96-well plates or 12x8 strips are pre-coated with capture Ag/Ab
Analytes	IgM or Ag detection, validated for Eurasian clades IV-VII	IgM and Ag detection, validated for Eurasian and African clades I-VII
Time to Result	≤6 hours for 1x 96-well plate: 12 batched samples (including dilution series)	≤6 hours for 3x 96-well plates: 36 batched samples (including dilution series)
Specimen Type	Plasma, serum	Plasma, serum, whole blood, saliva (breastmilk)
Sample Input	≤5 mL venepuncture	≤200 uL
Sample Preparation	Manual (conventional) centrifugation and dilution of specimen for use in BSL-3/4	Inactivation protocol for use in BSL-2 sample preparation
Test Output	Qualitative (positive, negative) result as defined by signal (S) relative to an empirical cutoff (CO) established for each assay run	Semi-Quantitative (sample to cut-off value, S/CO) for calibrator dilution series
Limit of Detection (LOD)	Empirical cutoff (CO) for each assay run using positive and negative controls	Reference (statistical) methods to define an assay cut-off
Linear Range (LOQ)	Defined by "normal range" of positive specimen control dilution series	
Clinical Sensitivity	>85%	>90%
Clinical Specificity	>85%	>95%
Cross Reactivity	Minimal but characterized cross-reactivity with other endemic or syndromic pathogens	
Interfering Substances	No interference for individual or mixtures of analytes, endogenous/exogenous substances	
Assay Process Controls and Calibration[g]	Each run includes positive and negative controls – not supplied with kit	Each run includes positive and negative controls - lyophilized controls included in kit
Third-Party Instrumentation	Manual ELISA plate washer and reader, calibrated pipettors; IPC sets, laboratory boxes, ventilation/negative pressure	Automated ELISA plate washer, reader

[g] Calibrated to international standard when available

Opened Kit Stability	Diluents stable at 2-8°C until expired; reagent dilutions stable at RT for 1 working day	
Unopened Kit Storage and Shelf Life	-20°C (or dry ice) for transport and up to 6 months storage	Kit reagent stability 2-8°C for transport and up to 12 months storage
Biosafety/Disposal Requirements	Biohazard disposal as appropriate for potentially infectious material	Specimens deactivated and sealed within cartridge/microplate; biohazard disposal (as appropriate)
Kit Certification	ISO 13485:2016 certified	ISO 13485:2016 certified; WHO PQ or CE or FDA approved
Price of Single Test	≤$15 USD at volume production	≤$10 USD at volume production

TPP 3: CCHF RDT

RDTs are ideal screening tests, suitable for field testing and triage in low infrastructure settings. RDTs have been used to effectively screen and triage suspected high-risk cases of diseases such as Ebola and dengue [20,21], a RDT for screening of active CCHFV infection would be valuable.

Specification	Minimal Performance	Optimal Performance
Intended Use	Rapid lateral flow immunoassay (RDT) for detection of CCHFV-specific human IgM or CCHFV Ag in human specimens for evidence of active CCHFV infection	Rapid lateral flow immunoassay (RDT) for detection of CCHFV-specific human IgM and CCHFV Ag in human specimens for evidence of active CCHFV infection
Kit Overview	Kit includes rapid test cassette, buffer/developer solution, disposable transfer pipette	
Analytes	IgM or Ag detection, validated for Eurasian clades IV-VII	IgM and Ag detection, validated for Eurasian and African clades I-VII
Time to Result	≤30 minutes	≤10 minutes
Specimen Type	Plasma, serum (venepuncture)	Plasma, serum, whole blood (venepuncture and fingerstick)
Sample Input	≤100 uL of specimen	≤30 uL of specimen
Sample Preparation	Serum or plasma separation	None
Test Output	Qualitative: detected/not detected visual readout compared to full process control line	
Limit of Detection	Empirical cutoff (CO) established for each assay run using positive control	Signal detected over background at clinically relevant minimum
Linear Range	Defined by "normal range" of positive specimen control dilution series	
Clinical Sensitivity	>80% IgM, Ag	>90% IgM, Ag
Clinical Specificity	>90% IgM, Ag	>95% IgM, Ag
Cross Reactivity	Minimal but characterized cross-reactivity with other endemic or syndromic pathogens	
Interfering Substances	No interference for individual analytes, endogenous/exogenous substances	
Assay Controls and Calibration	Full process internal control, external positive/negative controls (not supplied with kit)	Full process internal control, external positive/negative controls (lyophilized, included in kit)

Third-Party Consumables	Timer, materials required for venepuncture or fingerstick	
Opened Kit Stability	Stable at 18-30°C for 1 working day	Stable at 15-40°C for 1 working day
Unopened Kit Storage / Shelf Life	Kit reagent stability 2-30°C for transport and up to 6 months storage	Kit reagent stability 2-30°C for transport and up to 12 months storage
Biosafety/Disposal Requirements	Biohazard disposal as appropriate for potentially infectious material	
Kit Certification	ISO 13485:2016 certified	ISO 13485:2016 certified; WHO PQ or CE or FDA approved
Price of Single Test	≤$15 USD at volume production	≤$10 USD at volume production

Conclusions

The WHO R&D Blueprint for Action to Prevent Epidemics and the R&D Roadmaps are intended to focus international R&D effort for medical countermeasures, and reduce the time for new medical technologies to reach affected countries in a public health crisis. Following the identification and prioritization of the diagnostics outlined in the 2019 CCHF R&D Roadmap, the development priorities for CCHF testing have been further described here as target product profiles (TPP).

The TPPs in this document are intended to catalyze the development of diagnostic tests to detect active CCHFV infection, specifically for early detection of regional and globally circulating clades in the event of an outbreak. TPPs were developed for RT-PCR and ELISA tests that could be implemented in both centralized and decentralized settings (including a RDT TPP), and clinically validated across the broad geographic distribution of CCHF.

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Annex A

TPP for NPT Automated Platform

The TPP presented below is intended to provide platform specifications for decentralized, instrument-based testing for CCHF.

Specification	Minimal Performance	Optimal Performance
Platform Overview	Semi-automated platform with external sample preparation	Fully automated platform with integrated sample preparation
Throughput	Up to 20 samples per 8-hour day, capacity for random access (spot testing)	Up to 100 samples per 8-hour day, capacity for random access (spot testing)
Dimensions	Benchtop approx. 60 cm x 60 cm, <60 kg	Benchtop approx. 30 cm x 30 cm, <20 kg
Power Requirements	110-220 V AC, external/internal UPS	110-220 V AC
Data Readout	Visual readout via on-board or attached computer display	Same as minimal, including on-board algorithms for data interpretation with simple 'final result' readout and connectivity to data network for direct data transfer
Training Required	<5 days training for skilled laboratory technicians	<3 days for minimally skilled medical personnel (minimal laboratory training)
System Maintenance	Daily preventative maintenance <30 min; Mean time between failures: 12 months or 10,000 tests	Weekly preventative maintenance <30 min; Automated alert for errors or warnings; Mean time between failures: 24 months or 20,000 tests
System Calibration	Annual service call for calibration	Remote calibration service
Connectivity	USB interface, Integrated Local Network (LAN) port, local printer port.	Same as minimal, also supports connectivity to data network with end-to-end encryption.
Sample ID and Tracking	None – manual sample identification and tracking	Software-enabled unique identifiers for assay and sample, with accessory barcode, RFID, or other reader
Environmental Stability	Operation within 15°C-30°C	Operation within 10°C-40°C
Platform Certification	ISO 13485:2016 certified	ISO 13485:2016 certified; WHO PQ or CE or FDA approved
List Price of Platform	<$50,000 USD	<$25,000 USD