High-priority target product profile for hepatitis C diagnosis in decentralized settings:

Report of a consensus meeting

22 April 2015

Vienna, Austria

FIND
Because diagnosis matters

Forum for Collaborative HIV Research

Acknowledgements

This document was prepared by Alessandra Trianni (FIND), Nivedha Paneer (Forum for Collaborative HIV Research) and Claudia Denkinger (FIND) with input from other stakeholders. The document summarises consensus achieved at a meeting on high-priority target product profiles for new hepatitis C diagnostics in decentralized settings, convened by FIND and the Forum for Collaborative HIV Research. The document is based on target product profiles that were developed before the meeting by FIND and the Forum for Collaborative HIV Research, with support from the U.S. Centres for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), Partners in Health, the World Health Organization (Global Hepatitis Programme and Prequalification Programme), the Treatment Action Group (TAG) and other stakeholders.

This document was finalized following consideration of all comments and suggestions made by meeting participants.

The meeting contributions of the following individuals are gratefully acknowledged: Veronica Miller (Forum for Collaborative HIV Research), Philippa Easterbrook (WHO) and Teri Roberts (MSF).

Note to the reader

Because of the richness of the discussion, and in an attempt to keep this report simple and readable, comments have not been attributed unless their content rendered attribution necessary. This report aims to convey the themes addressed in each session, rather than attempting to provide a chronological summary of the dialogue.

Table of contents

Executive summary

Among the 184 million people worldwide who are HCV antibody positive [1], approximately 136 million are viraemic and have active chronic hepatitis C (HCV) infection. However, less than 1% of people infected in low- and middle-income countries (LMIC) are aware of their infection. A lack of effective diagnostics is one of the major barriers to providing life-saving care and treatment for hepatitis C.

Health care systems in LMIC are often unable to use existing diagnostic tests because they are complex, costly and require sophisticated infrastructure. Several promising diagnostics are under development, and diagnostic manufacturers need guidance on the type of HCV diagnostics they should invest in and the optimal test characteristics to have the greatest impact on HCV diagnosis and treatment in LMIC.

A meeting convened by FIND and the Forum for Collaborative HIV Research in Vienna on April 22, 2015 aimed to build consensus around two target product profiles (TPPs) that were identified by stakeholders to be of high priority for decentralized settings:

- HCV nucleic acid amplification test (NAAT) for the diagnosis of active HCV infection;
- HCV core antigen (cAg) test for the diagnosis of active HCV infection.

Different characteristics included in the TPPs were grouped into scope of use, performance and operational characteristics, and price. For each characteristic, participants were presented with a minimal and optimal solution.

Stakeholders were surveyed before the meeting through a Delphi-like process to facilitate consensus building around TPPs. In total, 50 stakeholders from 19 countries, NGOs, civil society, the pharmaceutical and *in vitro* diagnostics industries, and donors were asked to participate in this process. Thirty-six responded to the NAAT TPP (response rate 72%) and 26 responded to the cAg TPP (response rate 52%). A pre-specified level of agreement of 50% was achieved for all characteristics. Characteristics that achieved an agreement of less than 75% were discussed at the consensus meeting in Vienna. All stakeholders that were queried in the Delphi-like process were invited to participate in the meeting. Further discussions at the meeting built consensus on the majority of characteristics. Pricing was the characteristic with the least agreement among participants for both TPPs.

Key points arising from the discussion included:

- HCV diagnostic integration is important in health centres where patients at risk for HCV are evaluated and treated (e.g. drug treatment programmes, STD and HIV clinics). Ideally implementation for screening in the community should be feasible.
- Polyvalent platforms that test for HCV and other diseases, such as HIV, TB or hepatitis B are preferable.
- The minimum and optimal characteristics envisioned by stakeholders were similar for molecular and antigen-based tests.
- TPPs need to be considered in the context of different types of testing algorithms (i.e. a one test versus two-step process comprising a serology test followed by a confirmatory test).

Following the meeting and as a result of the discussion, a single revised TPP for HCV diagnostics was produced. It is included in this report.

Introduction

Among the 184 million people worldwide who are seropositive for hepatitis C virus (HCV), approximately 136 million are RNA PCR positive and have active chronic HCV infection [1]. HCV is curable, and effective treatment may decrease the risk of severe liver complications by over 80%, even in cirrhotic and HIV co-infected patients [2]. The treatment landscape for HCV is undergoing a dramatic transformation, from complex interferon-based regimens with high complication and limited cure rates, to simple, short regimens with higher tolerability and cure rates. High-income countries already have access to potent, well-tolerated, all-oral regimens that achieve cure rates of >90% within 12 weeks. Large-scale manufacturing of new regimens could result in a price drop to US$ 100-250/course (currently US$ 84,000 in the USA or US$ 900 under preferential pricing for 90 limited-resource countries for 12-weeks of Sofosbuvir alone). This offers a unique opportunity to address the epidemic in LMIC that have so far not prioritized the fight against HCV. Egypt has demonstrated that combating HCV is cost-effective in limited-resource settings and feasible on a programmatic scale, and many countries are interested in following this example.

However, the major bottleneck to appropriate HCV care is diagnosis. Firstly, diagnostic capacity in LMIC is very low and mostly in the private sector, with <1% of patients in LMIC even aware of their infection [3]. Secondly, existing diagnostic algorithms are complex and tests are not appropriate for LMIC. In addition, current tests for hepatitis C, such as serology, have variable accuracy in HIV co-infected patients, while molecular tests are costly and availability is limited to only a few highly experienced, centralized settings [4].

Several promising diagnostics are under development and diagnostic manufacturers need to know the type of HCV diagnostics they should invest in and the optimal characteristics of these tests. The development of target product profiles (TPPs) is useful to align the needs of end users with the targets and specifications that product developers need in order to meet the performance and operational characteristics of a test. An informal priority-setting exercise was carried out in 2014 through stakeholder consultation to identify the key needs that should be the highest priority for further TPP development.

The potential models for delivering hepatitis C care and treatment include delivery through a centralized or decentralized infrastructure. Currently, tests confirming HCV infection (either molecular or antigen-based) are only available in centralized settings, if at all, and samples need to be transported to the laboratory from the sites where patients present for care. Several countries with high HIV burdens are optimizing their centralized molecular infrastructure with improvements in sample transport logistics and usage of dried blood spots. As platforms for HIV are often also equipped to do HCV testing (using polyvalent platforms, e.g. Roche Taqman), there is the potential to use existing infrastructure established for HIV also for HCV.

Point-of-care (POC) platforms (i.e. platforms where patients present for diagnosis and treatment) may also play an important complementary role because many countries favour a decentralized or a combined centralized/decentralized infrastructure due to difficulties with sample transfer. Also, the advantages of rapid turn-around times offered by POC platforms may reduce loss to follow-up and allow for immediate treatment decisions [5]. As centralized platforms are already available, the focus of TPP development was on the diagnosis of HCV in decentralized settings.

The potential market of a test for detection of active disease alone could be estimated as follows: More than 184 million people worldwide are seropositive for HCV [1], and given spontaneous clearance rates of 26% [6], approximately 136 million individuals are chronically infected with HCV. If at least 10 patients are tested for every case identified, this translates into over one billion tests needed to curb the global HCV epidemic.

Developing target product profiles

Manufacturers need TPPs at an early stage in the diagnostic development process to inform the targets and specifications for the performance and operational characteristics of a test that will also meet the needs of end users. At a minimum, the TPPs for diagnostic tests should specify the goal to be met (e.g. to initiate treatment), the target population that will be tested, the level of implementation in the health-care system and the intended end users. In addition, TPPs should outline the most important performance and operational characteristics as well as pricing (with the term "minimal" used to refer to the lowest acceptable output for a characteristic and "optimal" used to refer to the ideal target for a characteristic). The optimal and minimal characteristics define a range. Products should meet at least all of the minimal characteristics and preferably as many of the optimal characteristics as possible.

Currently, confirmation of disease and monitoring of treatment success is performed primarily with a NAAT test that detects HCV RNA. Alternatively, a core antigen (cAg) test can be done. HCV cAg is detectable in the blood stream one to two days after HCV RNA appears [7] and in the "window phase" of infection where individuals are viraemic but lack antibodies to HCV [8]. In treated individuals, 1pg/ml of cAg corresponds with 7,900 IU/ml of HCV RNA [9] with a high correlation between HCV RNA and core Ag seen at RNA levels greater than 10^3 IU/ml for all genotypes [10, 11]. During HCV treatment monitoring, cAg decreases correlate with decreases of HCV RNA levels [12]. Thus, HCV cAg represents a sufficient substitute for HCV RNA for diagnosis of active infection and treatment monitoring.

In early 2015, the following TPPs were developed by the Forum for Collaborative HIV Research and FIND based on the priorities identified by stakeholders in 2014 and further input from several stakeholders (from the U.S. Centres for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), Partners in Health, the World Health Organization (Global Hepatitis Programme and Prequalification Programme), the Treatment Action Group (TAG) and a technical advisory group (composed of members from FIND and MSF):

- HCV nucleic acid amplification test (NAAT) for the diagnosis of active HCV infection;
- HCV cAg test for the diagnosis of active HCV infection.

The initial TPPs were detailed and incorporated information about a comprehensive list of performance and operational characteristics. The development timeline envisioned in the TPPs was five years. For several of the characteristics, only limited evidence was available and further expert advice was sought from about 15 stakeholders.

In order to develop a more comprehensive stakeholder opinion, a larger stakeholder audience was engaged in collaboration with WHO, including clinicians, implementers and representatives of countries and national HCV programmes, and the diagnostics and pharmaceutical industries.

To meet this aim, a consensus-gathering meeting was convened by FIND and the Forum for Collaborative HIV Research on April 22, 2015 in Vienna, Austria. For the purpose of the meeting, key characteristics for each of the TPPs were identified in order to shorten the TPPs and facilitate the consensus-building process on the most important characteristics.

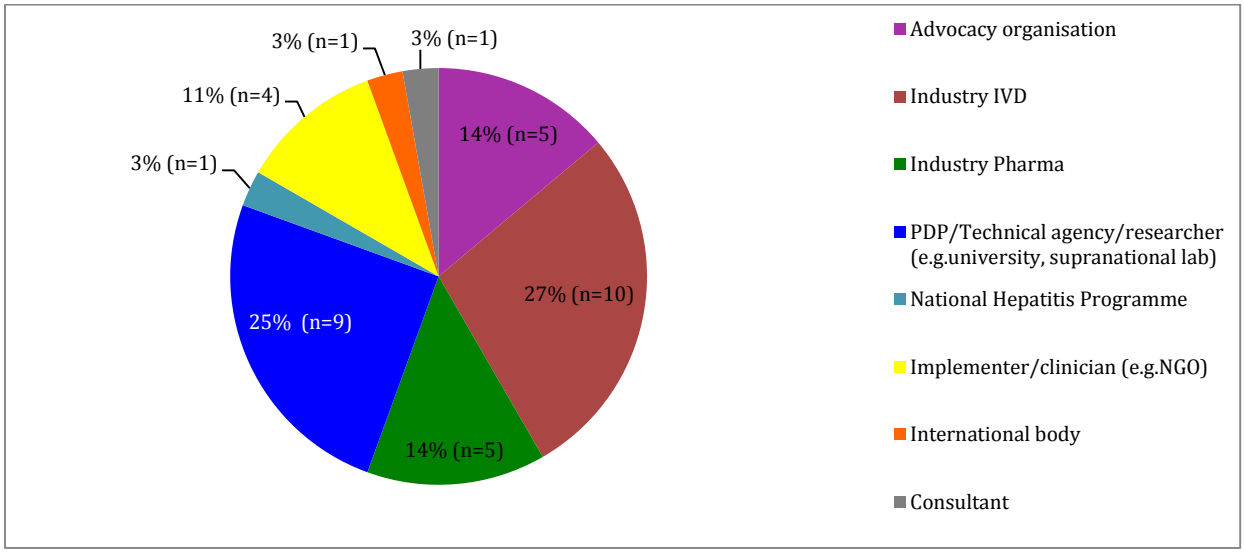
Delphi-like process

In the months prior to the meeting, a Delphi-like process was used to facilitate consensus building. The shortened TPPs were sent to all invited participants. Participants were requested to provide a statement on their level of agreement with each of the proposed characteristics for each TPP. Agreement was scored on a Likert scale ranging from 1 to 5 (1=disagree, 2=mostly disagree, 3=do not agree or disagree, 4=mostly agree, 5=fully agree).

Consensus was pre-specified at greater than 50% of respondents providing a score of at least 4 on the Likert scale. In total, 50 organizations/individuals (see Appendix A) were asked to participate in this process, of whom 36 responded to the NAAT TPP (response rate, 72%) and 26 to the cAg TPP (response rate, 52%).

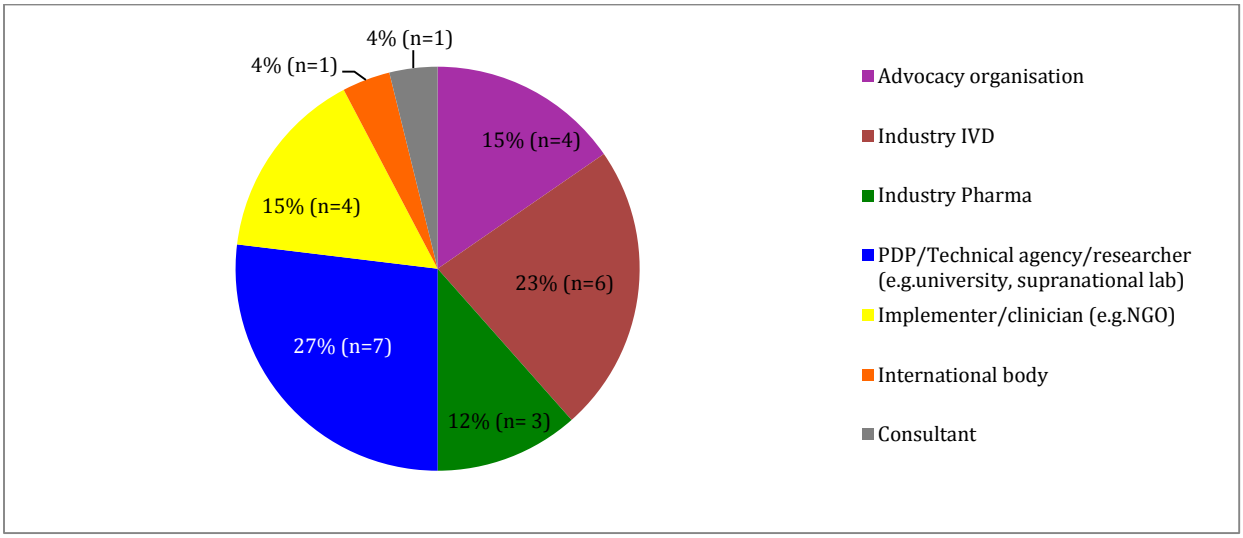
For the NAAT TPP, about half of responders were from the *in vitro* diagnostics industry or product development partnerships/technical agencies/researchers (27% and 25% respectively), 14% were from advocacy organizations and the same from the pharmaceutical industry, 11% were implementers/clinicians and the remainder (3% each) represented national hepatitis programmes, international bodies and consultants (see Figure 1 below).

Figure 1: Organizational affiliation of 36 respondents to NAAT TPP



For the cAg TPP, the 27% of responders were from product development partnerships/technical agencies/researchers, 23% from the *in vitro* diagnostics industry, 15% from advocacy organizations and implementers/clinicians, 12% from pharmaceutical industries, 4% were from international bodies and consultants (see Figure 2 below).

Figure 2: Organizational affiliation of 26 respondents to cAg TPP



Initially, two rounds of the Delphi-like survey had been planned, but since predefined consensus for all characteristics was reached after the first round, a second round was not initiated. The level of agreement and the comments made in the Delphi-like survey are presented in Appendix A.

There was agreement on the following characteristics: goal of the test, target user, setting for implementation (health system level), specificity and all operational characteristics. The final characteristics are presented in the revised TPP below. Characteristics on which fewer than 75% of the respondents agreed, or on which a distinct subgroup disagreed, were discussed during the consensus meeting in Vienna.

Consensus meeting

The April 22, 2015 meeting in Vienna focused on building further consensus on areas of discrepancy in opinion around the two high-priority TPPs.

All stakeholders that were sent the Delphi-like survey were invited to the meeting. Thirty-five participants were able to attend. Participants comprised country representatives, stakeholders from technical and funding agencies, researchers, implementers and civil society organizations, and representatives from companies working on HCV diagnostics and drugs (see Appendix B for the participant list). The following summarizes the discussion at the meeting.

Target population

In the proposed TPPs, only countries with medium to high HCV prevalence (1.5-3.5% and >3.5%, respectively) were considered as a target population. During the discussion, the point was made that high-risk populations in low-prevalence settings should also be included as a target population. These high-risk populations include: people who inject drugs, people living with HIV, prisoners, people with tattoos, sex workers, men who have sex with men, people with frequent contact with the health-care system (i.e. the chronically ill) and pregnant women. In order to achieve the long-term goal of HCV elimination, optimally the test should be performed on all asymptomatic patients in primary-care settings or in the community. One stakeholder pointed out that, in many settings, testing will remain only in the private sector unless urgent investments are made to build public sector programmes.

Sensitivity *(see glossary in Appendix D for description of terms)*
In the proposed TPPs, the ideal analytical sensitivity was defined as 15 IU/ml for both NAAT and cAg, while the minimal TPP was defined as 1000 IU/ml for both. Currently, the most sensitive cAg test on the market is the Abbott Architect, which has an analytical sensitivity of about ~1000-3000 IU/ml=~= 3fmol/L). Translating the minimal sensitivity into diagnostic sensitivity means that about 5% of individuals with levels of viraemia less than 3,000 IU/ml would be missed [13]. The opinion amongst the stakeholders was that this is unlikely to have major programmatic impact. Even if a test with a diagnostic sensitivity similar to that of Abbott's misses some patients, it is likely "*good enough"*. This is certainly true from a population perspective, where any test with 95% sensitivity reaching patients that currently do not have access to diagnosis and treatment would be a substantial step forward. Further, it was suggested that an optimal sensitivity of 200 IU/ml would likely be sufficient, although this needs to be validated in larger surveillance studies detecting viral load. Certainly, if the optimal sample type were considered (i.e. capillary blood), a lower sensitivity (i.e. < 200 IU/ml) would not be technically feasible.

Confirmation of cure and timing of test of cure
Additional points need to be addressed when using the same test for diagnosing infection and monitoring treatment success. Treatment monitoring does not appear to be necessary or useful with novel direct-acting antiviral agent (DAA)-based regimens, as the early reduction in viral load does not correlate with cure [14]. When considering a test of cure at the end of DAA-therapy, the optimal time at which to perform this test is currently unclear. Trial results using novel DAAs suggest a viral rebound at an earlier time point after unsuccessful treatment compared to interferon-based therapy [15, 16]. Sidharthan and co-authors showed that the presence of low amounts of HCV RNA at end of treatment with DAAs was not predictive of SVR at 12 weeks [14]. Thus, a test of cure would possibly be more appropriate six to eight weeks after end of therapy. A limit of detection (LOD) of 1000 IU/ml will likely be sufficient to rule out viral rebound at that time point but this needs to be further confirmed in future studies.

Quantitation
In the proposed TPP, quantitation was determined not to be necessary for NAAT and cAg if novel DAAs are used, as response-guided therapy (as practiced with interferon-based regimens) is not necessary. During the discussion, participants commented that the cost differential between a qualitative and quantitative test was small or absent, and the benefit of a quantitative test is that it allows research questions to be investigated. Hence, it was concluded that qualitative should be the minimal acceptable output, while quantitative should be the optimal.

Price of the test
The discussion on price had the lowest level of agreement. As in the Delphi-like survey, some stakeholders commented that the maximum and minimum prices (ex-works, at scale) as proposed in the current TPP were too high (especially for LMIC). Many industry respondents, however, indicated that prices were too low. During the discussion, the main factors that drive the price of tests were defined. First, the complexity of the supply chain, which includes but is not limited to shipping costs, import taxes, customs charges and local distribution costs, results in much higher end-user prices than the cost of goods sold by the manufacturer. Different supply chain models for LMIC should be explored to reduce the costs incurred by end users. For this to happen, cost transparency from manufacturers on cost of goods to local distributors is necessary. This is currently being attempted for the roll-out of HCV diagnosis in Mongolia. Second, the complexity of the test contributes to higher test cost. For example, labour-intensive sample preparation for detection of HCV cAg was mentioned as a driver of higher costs. Third, lower demand for HCV diagnostics as compared to diagnostics for other diseases is another driver for higher cost of HCV diagnostics. Costs defined in the TPP were defined based on at-scale use. Pooled procurement and forecasting were identified as possible solutions to reduce pricing. Possibilities to decrease price of diagnosis and care also include integration within care for other diseases, such as HIV, TB and also hepatitis B in health centres. This can leverage investments made in polyvalent platforms and care infrastructure. Finally, one stakeholder pointed out that one main challenge for achieving robust and low-cost HCV diagnostics is the lack of a globally funded initiative for negotiating

reduced costs for HCV diagnostics, which results in national governments needing to negotiate one-on-one with the manufacturer to procure diagnostics for their country.

Polyvalency
It is crucial to integrate HCV diagnosis and treatment with other diseases, such as HIV, TB and hepatitis B, in health centres. Participants encouraged the development of polyvalent platforms that can diagnose multiple diseases, including HCV. Multiplexing (i.e. testing of different analytes from the same sample) would be advantageous for some tests but is not necessary.

Other needs
Independent of the described TPP for a decentralized test for diagnosis and monitoring of treatment success, two other needs were clearly identified:

- Validation and regulatory approval of dried blood spots for use on centralized platforms for both qualitative/viral load testing and genotyping (while we still need it); and
- Improved quality serology-based point-of-care assay (rapid diagnostic test) for screening (including polyvalent assays for HIV/HCV) that is affordable (<US$ 2 per test) and retains accuracy in co-infected individuals.

Research questions

As part of the discussion, the following research questions were identified:

1. The current Abbott Architect HCV cAg assay misses approximately 5% of chronically infected individuals. However, the long-term outcomes of individuals with low-level antigenaemia / viraemia have not been sufficiently studied. What are the characteristics of HCV-infected individuals with < 1000-3000 IU/ml who are missed by the cAg assay? Are they less prone to develop HCV disease, or do they still have notable disease progression that would make them eligible for treatment? Are they more likely to resolve their infection?

2. There is uncertainty about when a test for cure should be done because it seems the viral rebound in the relapse phase is faster than with the peg-interferon-based regimens. It can also be considered whether a test of cure is necessary at all given the high efficacy of novel regimens, or the test of cure could at least be deprioritised.

3. Better surveillance data, including data on viral load at diagnosis in HCV-infected patients and at different time points after treatment in patients who do not achieve an SVR, are needed to define optimal sensitivity cut-offs.

4. Would it be better to have a monitoring test to differentiate between those that fail because of therapeutic failure and those that adhere poorly?

5. It would be useful to understand what diagnostic sensitivity would be achieved with an optimal analytical sensitivity of 200 IU/ml and a minimal analytical sensitivity of 5000 IU/ml.

6. What is the cost effectiveness of a one-step approach versus a conventional two-step approach (with antibody test first followed by RNA NAAT or cAg) in different prevalence settings?

Revised target product profile for a test for diagnosis of active HCV infection and test of cure

During the discussion, the following key points were made:

- HCV diagnostic integration is important in health centres where diagnosis and treatment for other diseases are provided (e.g. HIV, drug treatment programmes). Thus it would be favourable for platforms to be capable of doing multiple different tests (e.g. HIV and HCV).
- Characteristics were similar for both TPPs, independent of whether the test envisioned was a molecular or antigen-based test. Therefore, a combined revised TPP has been created.
- TPPs need to be considered in the context of different types of testing algorithms (one-step versus two-step).

As a result, only a single revised TPP was defined, focusing on the characteristics related to the diagnostic algorithms in which a test would be used. In the revised TPP, the goal of the test continues to be the diagnosis of active, viraemic HCV infection. Furthermore, the test should be usable to confirm cure upon treatment completion. Two algorithms were considered (see Figure 3 below, and refer to the glossary in Appendix D for definition of terms):

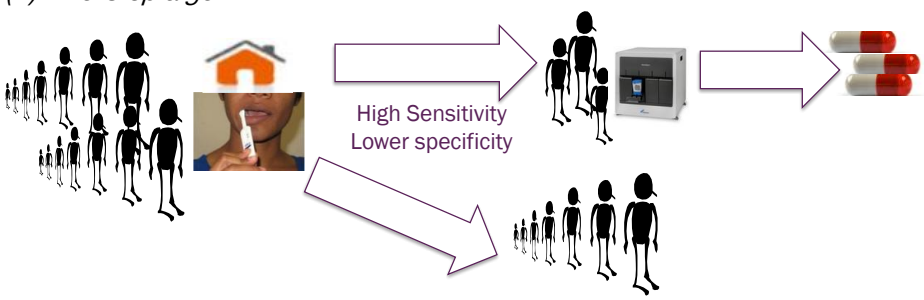
(A) One-step: cAg test or molecular test
(B) Two-step: Serological test followed by a confirmatory test (either antigen-based or NAAT)

The suitability of a one- versus two-step algorithm depends on the local prevalence, the performance of the test and the cost of the algorithm.

Figure 3: One-step and two-step algorithms for HCV

(A) One-step algorithm:

(B) Two-step algorithm:



Limitations of the TPP: The TPP reflects the opinion of the stakeholders represented in the Delphi-like survey and at the meeting. While we attempted to have a large group of stakeholders that was representative of all the different groups, not everybody was able to participate. Thus, consultation of a larger group and specifically more implementation partners and country programmes (either in the form of a survey or in the form of a face-to-face meeting) could be considered.

Table 1: Combined TPP for an HCV test using input from the Delphi-like survey and discussions at a consensus meeting, 22 April 2015

Characteristic	Optimal	Minimal	Rationale and evidence
SCOPE			
Goal of test	The goal of the test is two-fold: 1. To diagnose active viraemic HCV infection (new or reinfection) and provide baseline virological assessment (quantitative or qualitative); 2. To confirm cure upon treatment completion. Ideally, the test would be done with the purpose of initiating treatment within the same clinical encounter or the same day. Not intended for blood screening. The timeline of development for tests envisioned in the TPP is 5 years.	The goal of the test is two-fold: 1. To diagnose active HCV viraemic infection (new or reinfection) and provide baseline virological assessment (qualitative) with the purpose of initiating treatment; 2. To confirm cure upon treatment completion. Not intended for blood screening. The timeline of development for tests envisioned in the TPP is 5 years.	Detection can be performed by NAAT or by antigen detection. Presence of HCV RNA or core antigen in a patient is indicative of active HCV infection. Currently, the HCV RNA or cAg test is performed after a positive anti-HCV serological test (i.e. two-step algorithm). Conceivably, provided the prevalence is substantial and the cost of the NAAT or cAg test is low, either test could be used in a one-step algorithm.
Target population	• Countries with a medium to high prevalence of HCV (1.5-3.5% and >3.5%) • High-risk populations in low prevalence settings (<1.5%). These high-risk populations include: persons who inject drugs or have used intranasal drugs (PWID), people living with HIV (PLWH), men who have sex with men (MSM), prisoners, people with tattoos, sex workers, people with frequent contact with the health-care system (i.e. chronically ill) and		

Characteristic	Optimal	Minimal	Rationale and evidence
	children born to HCV-infected mothers. In order to achieve the long-term goal of HCV elimination, optimally the test should be performed on all patients in primary care settings, antenatal clinics and in community screening programmes.		
Target operator of test	Community workers with minimal training	Health-care workers or laboratory technicians with limited training (i.e. able to operate an integrated test with minimal additional steps)	
Lowest setting for implementation (public & private)	Community centres	District hospital (Level II)	
PERFORMANCE CHARACTERISTICS			
Diagnostic sensitivity (comparison with NAAT reference standard in plasma)	>99%	90%-95%	Rationale of optimal: Ideally a test should be as sensitive and specific as available plasma-based HCV NAAT tests. A commonly used reference standard is the VERSANT HCV RNA Qualitative Assay, which is FDA-approved for diagnosis of active HCV infection (although the VERSANT HCV RNA Qualitative Assay is being taken off the market, it remains the most analytically sensitive assay and was used as the gold standard in most instances). Rationale of minimal: If a test is easier to implement at lower levels of the health care system without requiring substantial technical expertise or complex laboratory infrastructure, and is less costly, then a compromise can be made on sensitivity. A test with a suboptimal sensitivity of 90-95% with improved operational characteristics was considered acceptable by stakeholders as it would improve rates of diagnosis substantially over what is currently possible. However, no studies or modelling have been done on the minimal acceptable sensitivity and

Characteristic	Optimal	Minimal	Rationale and evidence
			the optimal other characteristics needed by a test for HCV diagnosis to lead to substantial improvement in HCV detection on a population level. Modelling work for TB has provided insights that could potentially be applicable for HCV as well. A model showed that for the WHO Southeast Asia Region a POC biomarker test with a sensitivity of 50% for smear-negative TB, if employed at the most peripheral health-care setting, would result in a similar reduction in TB incidence as a test with 70% sensitivity for smear-negative TB that would be employed at the district level (e.g. Xpert MTB/RIF) [17]. However, the exact trade-off between a lower sensitivity (for smear-negative TB) and an increase in access to testing is setting dependent. Under the minimal scenario, some patients would be incorrectly diagnosed as not having active HCV infection, What impact that would have on patient and provider behaviour is unclear.
Analytical sensitivity (comparison with NAAT reference standard)	200 IU/ml	1000-3000 IU/ml	Among the majority of infected individuals with chronic HCV infection, HCV RNA viral loads are between 10^4 and 10^7 IU/ml [13]. In studies of viral dynamics during acute infection, viral loads as low as 3 log IU/ml (or 1000 IU/ml) were seen during the first four months after infection [13]. The optimal LOD of 200 IU/ml should therefore detect most patients (>99%). At a minimum, analytical sensitivity of 1000-3000 IU/ml or 3 fmol cAg/l (current LOD of the Abbott HCV cAg assay), the corresponding clinical sensitivity should be 90-95%. Upper limit of the dynamic range should be equivalent to that of current laboratory-based quantitative HCV NAAT tests. A NAAT assay should be standardized with the WHO International Standard for Hepatitis C Virus RNA, as has been done with

Characteristic	Optimal	Minimal	Rationale and evidence
			current FDA-approved and CE-marked qualitative and quantitative HCV NAAT assays. Interestingly, HCV cAg test have been shown to be negative among a portion of untreated individuals with high HCV RNA levels, indicating the likely presence of mutant variants [18]. The limitation of the cAg assay to accurately detect these variants may present a challenge to elimination. Data from patients who relapsed after treatment with peg-interferon and ribavirin therapy indicate that HCV rebounds quickly to high levels (10^3 IU/ml and greater) within a few weeks after the end of treatment [19]. Early data from DAA-based therapy suggests that an even more rapid relapse would happen (unpublished data; communication with A. Hill). Given the high correlation between HCV cAg and HCV RNA levels, either test would likely be suitable for monitoring virologic response after treatment completion several weeks after completion of therapy.
Diagnostic specificity (comparison with NAAT reference standard)	>99%	>98%	Since the test is a test for detection of active HCV infection, it should be as specific as current commercially available and FDA-approved HCV NAAT tests to avoid false positive results [20].
Analytical specificity – HCV detection	No cross reactivity with endogenous substance and exogenous factors (e.g. HIV-1, HIV-2, HBV, HEV, antimalarials, anti-TB, ART)	No cross reactivity with endogenous substance and exogenous factors (e.g. HIV-1, HIV-2, HBV, HEV, antimalarials, anti-TB, ART)	
Polyvalency	Ability to detect HIV, hepatitis B on the same instrument		

Characteristic	Optimal	Minimal	Rationale and evidence
Quantitation	Quantitative	Qualitative	Treatment monitoring is not considered necessary or feasible with novel DAA agents [14], therefore a qualitative test result is preferred. According to stakeholder opinion, a quantitative result would be beneficial as it allows research questions to be investigated; however, it cannot come at an increased cost.
OPERATIONAL CHARACTERISTICS			
Specimen type	Capillary whole blood	Venous whole blood or plasma	The emphasis is for the use of capillary whole blood that can diagnose infection in the clinic without requiring additional laboratory equipment such as a bench top centrifuge. The need for phlebotomy to draw venous whole blood would limit the applicability of the test in lower settings of care as per stakeholder opinion. If plasma is to be a specimen type (minimal criteria), the plasma separation step should be integrated into the instrument.
Specimen prep (total steps)	Integrated specimen preparation (including plasma separation if needed); less than 2 steps required (no precision volume control and precision time steps)	Maximally 2 steps (no precision volume control and precision time steps)	Equipment such as a centrifuge or heat block are available only infrequently at level 1 health centres and some district hospitals, and therefore should not be required for novel assays. Expertise to operate a precision pipette is also often lacking [21]. For the detection of cAg, several sample preparation steps are needed: i) to dissociate antibody-bound cAg; ii) to lyse viral particles and expose cAg; and iii) to inactivate antibody. These should also optimally be integrated with the test of detection.
Time to result	< 15 minutes	< 60 minutes	The need for a rapid turn-around time, the possibility for batching and/or random access for testing, and the testing of multiple specimens at the same time are interrelated. The time to result is probably the

Characteristic	Optimal	Minimal	Rationale and evidence
			most important parameter, as extending the wait time for patients will possibly result in loss to follow-up [22, 23]. Most current immune-chromatographic rapid tests produce results within 20 minutes. The ideal time to result has not been studied and might vary largely between countries and between settings where the patient is tested. But in order to be deployable as a test for POC, the result should be available within the same visit.
Specimen capacity + throughput	Multiple at a time; random access/parallel processing	One at a time (any external reagents should be aliquoted for one time use)	Preferred that one specimen does not occupy the instrument at a time - i.e., random access/parallel analysis. If the platform is multi-analyte, then running different assays should be feasible at the same time.
Biosafety + waste disposal	Mostly simple waste; minimal biosafety waste; no sharps	No need for a biosafety cabinet; consumables should be able to be disposed of as biosafety waste; simple trash.	Increased biosafety of a novel test will enhance acceptability of the test by providers. Further information provided in WHO Laboratory Biosafety Manual [24].
Instrumentation	Instrument-free	Allow for separate sample preparation device (e.g. mini-centrifuge)	The simpler, more portable and durable/robust the test is, the more likely it will be implemented in peripheral settings. Ideally an instrument free test (e.g. immunochromatographic test) would be the preferred optimal solution but this is likely not feasible with the analytical sensitivity that is necessary and a small sample volume from a fingerstick.
Power requirements	If device necessary then: battery-operated with recharging solution (e.g. solar) and circuit protector lasting up to 3 days of constant use and able to run off standard electricity	Rechargeable battery or solar power lasting at least 8 hours.	Continuous power is not always available at the level of a health and microscopy centre and even less likely at primary care clinics, therefore a battery-operated device with charge possibility conceivably through solar power would be most ideal in order for a test to fit into the entire breadth of settings [21, 23].

Characteristic	Optimal	Minimal	Rationale and evidence
Maintenance/ calibration	Disposable, no maintenance or calibration required If device necessary then: preventative maintenance at 2 years or >5,000 samples; include maintenance alert; remote calibration	Preventative maintenance at 1 year or >1000 samples; only simple tools/minimal expertise required; include maintenance alert. Swap-out of platforms permitted.	If a device is anticipated to have a longer lifespan, then a maintenance alert is essential to ensure proper functionality in settings where it is unlikely that the same person will always handle the device and records will be kept on duration of use. It is essential that only simple tools/minimal expertise are necessary to do the maintenance given that service visits are difficult outside of urban settings.
Data analysis	Integrated data analysis	Integrated data analysis (no requirement for PC); exported data capable of being analysed on a separate or networked PC.	
Connectivity	If device necessary then integrated connectivity; if no device necessary, then the test should allow data export via a separate reader. Full data export (on usage of device, error/invalid rates, and personalized, protected results data) over USB port and network. Network connectivity through Ethernet, WiFi, and/or GSM/UMTS mobile broadband modem. Results should be encoded using a documented standard (such as HL7) and be formatted as JSON text. JSON data should be transmitted through http(s) to a local or remote server as results are generated. Results should be locally stored and queued	Full data export (on usage of device, error/invalid rates, and personalized, protected results data) over USB port and network. Network connectivity through Ethernet, WiFi, and/or GSM/UMTS mobile broadband modem. Results should be encoded using a documented standard (such as HL7) and be formatted as JSON text. JSON data should be transmitted through http(s) to a local or remote server as results are generated. Results should be locally stored and queued during network interruptions and sent as a batch when connectivity is restored.	Data export will enhance surveillance, device and operator management and allow for supply chain management.

Characteristic	Optimal	Minimal	Rationale and evidence
	during network interruptions and sent as a batch when connectivity is restored.		
Result capture, documentation, data display	If instrument-free: ability to save results via separate reader. If device necessary: integrated results screen and ability to save and print results; USB port. On-instrument visual readout and the ability to add information (patient ID, operator ID, date location, etc.)	Ability to save results The test menu should be simple with integrated LCD screen; simple key pad or touch screen.	Results should be simple to interpret (positive/negative for HCV detection).
Operating temperature/ humidity/ altitude	Between +5°C to +40ºC at 90% humidity and at an altitude of 3000 metres	Between +10°C to +35ºC at 70% humidity and at an altitude of 2000 metres	High environmental temperatures and high humidity are often a problem in countries where HCV is endemic.
Reagent kit transport	No cold chain required; tolerance of transport stress for a minimum of 72 hrs at -15°C to +40ºC	No cold chain required; tolerance of transport stress for a minimum of 48 hours at -15°C to +40ºC	Refrigerated transport is costly and often cannot be guaranteed during the entire transportation process. Frequent delays in transport are commonplace.
Reagent kit storage/ stability	2 years at +5°C to +40ºC at 90% humidity & transport stress (72 hours at 50ºC); no cold chain required	12 months at +5°C to 35º C, 70% humidity, including transport stress (48 hours at 50ºC); no cold chain required	High environmental temperatures and high humidity is often a problem in many countries where HCV is prevalent.
Internal process quality control	Internal full-process control, positive control & negative controls	External positive control	In addition to compatibility with existing external quality assessment schemes

Characteristic	Optimal	Minimal	Rationale and evidence
PRICING			
Maximum price for individual test (reagent costs only; at scale; ex-works)	< US$ 5	< US$ 15	For a one-step solution, the cost needs to be low, as a trade-off in the ease-of-use/performance for price would not be accepted. Conversely, in a two-step solution, a higher cost is more likely to be accepted, as people would be willing to make a trade-off provided the overall cost of the algorithm remains low. Cost-benefit analyses are needed to explore different options. Trade-offs between optimal characteristics may be necessary to achieve optimal pricing. Preferences about acceptable trade-offs need to be further defined.
Maximum price for instrumentation	< US$ 2000	< US$ 20 000	The lower the price for instrumentation, the lower the up-front cost to a health-care system would be and thus the lower the barrier to implementation. Further modelling is necessary to confirm the maximal price estimated. Price should include warranties, service contracts and technical support. Alternatively, rental agreements for equipment should be an option.

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Appendix A: Delphi-like survey results for HCV target product profiles

Target product profile for an HCV nucleic acid amplification test for the diagnosis of active HCV infection

The test, as it was envisioned before the consensus meeting, would ideally be implemented in a health centre (Level I) where patients at risk for HCV are cared for (e.g. people who inject drugs (PWID), people living with HIV/AIDS (PLWH), men who have sex with men (MSM), incarcerated individuals). The test is intended both for diagnosis and as a test of cure. Given that quantitative monitoring is not required for novel regimens, qualitative NAATs are equally acceptable. The optimal limit of detection (LOD) is specified at 15 IU/ml (comparable to LOD of the VERSANT HCV RNA Qualitative Assay, which is FDA-approved for diagnosis). This cut-off will not only allow diagnosis of active infection (the majority of individuals with chronic infection have viral loads greater than 1000 IU/ml) but also enable the test to be used to monitor sustained virologic response (SVR). Capillary whole blood is the preferred specimen type to allow diagnosis in the same clinic visit without requiring additional laboratory equipment to obtain plasma and/or serum from whole blood. If plasma is to be a specimen type (minimal criteria), the plasma separation step should be integrated into the instrument.

The following table indicates the results of the Delphi-like survey across the different characteristics for an HCV NAAT test.

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
SCOPE					
1. Goal of test	Confirm active viraemic HCV infection and provide baseline virologic assessment (qualitative or quantitative) before treatment initiation	88% (92%-64%)	Confirm active HCV infection and provide baseline virologic assessment (qualitative or quantitative) before treatment initiation with the purpose of starting treatment	88% (92%-64%)	• Consider NAAT as all-in-one test to screen and confirm infection (if $ enough)

[1] Lower and upper bounds for the ranges were calculated by assuming stakeholders who did not respond to the TPPs would have agreed with the characteristics (score of 4 or higher, upper bound) or disagreed with the characteristics (score of 3 or lower, lower bound)

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
	with the purpose of starting treatment within the same clinical encounter (or same day). Monitor and confirm SVR upon treatment completion. Not intended for blood screening.		within the same clinical encounter (or same day). Monitor and confirm SVR upon treatment completion. Not intended for blood screening.		
2. Target population	Countries with medium to high HCV seroprevalence (1.5-3.5% and >3.5%, respectively, Hanafiah et al, Hepatology 2013) Target groups: Patients with HCV Ab+, special focus on PWID, PLWH, MSM, incarcerated individuals, persons who may have been exposed to contaminated	88% (92%-64%)	Countries with medium to high HCV seroprevalence (1.5-3.5% and >3.5%, respectively, Hanafiah et al, Hepatology 2013) Target groups: Patients with HCV Ab+, special focus on PWID, PLWH, MSM, incarcerated individuals, persons who may have been exposed to contaminated blood due to unsafe medical practices and children	88% (92%-64%)	• In generalized epidemics (e.g. Egypt, Mongolia, Pakistan), include people >50 years and those with frequent contact with health system

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
	blood due to unsafe medical practices and children born to HCV-infected mothers.		born to HCV-infected mothers.		
3. Target user of test	Health-care workers	92% (94%-66%)	Laboratory technician	88% (92%-64%)	• Include community health-care workers and voluntary sector workers with minimal training under optimal • What is considered "minimal training"? 2 days for health-care worker (optimal) and 1 day for laboratory technician (minimal) were suggested • Reliance on lab tech may limit testing scale-up
4. Setting for implementation (health system level)	Health centre (Level I)	86% (90%-62%)	District hospital (Level II)	83% (88%-60%)	• Health centres may not exist in all places; expand to include community settings, public health clinics, NGOs and private practices under optimal, but this may limit same-day diagnosis and treatment in certain cases. • District hospital implementation may not reach and manage all who need testing
PERFORMANCE CHARACTERISTICS					
5. Diagnostic sensitivity	>99%	83% (88%-60%)	>97%	77% (84%-56%)	• Split responses for diagnostic sensitivity • Lower sensitivities: 97-98% (optimal) and 90-92% (minimal) • Higher sensitivities: >99 • Minimal diagnostic sensitivity should align with minimal analytical sensitivity

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
6. Diagnostic specificity	>98%	88% (92%-64%)	>98%	86% (90%-62%)	• What is an adequate analytical cut-off for initial diagnosis? • Is 1000 IU/ml sufficient to determine cure? • Optimal LOD not achievable with capillary whole blood specimens • Current lab-based NAAT LOD: 15 IU/ml • Volume of fingerstick blood, 50µl→ LOD of ~300 IU/ml (optimal) • How much can we give up in assay LOD for convenience of capillary whole blood? Respondents >1000 – 5000 IU/ml
7. Analytical sensitivity	<15 IU/ml	80% (86%-58%)	1000 IU/ml	72% (80%-52%)	• Balance between feasibility of testing x specimens per substance for cross-reactivity versus statistically relevant results
8. Analytical specificity – HCV detection	No cross reactivity with endogenous substance and exogenous factors (e.g. HIV-1, HIV-2, HBV, antimalarials, anti-TB, ART)	92% (94%-66%)	No cross reactivity with endogenous substance and exogenous factors (e.g. HIV-1, HIV-2, HBV, antimalarials, anti-TB, ART)	92% (94%-66%)	
OPERATIONAL CHARACTERISTICS					
9. Specimen type	Capillary whole blood	97% (98%-70%)	Venous whole blood, plasma, serum	86% (90%-62%)	• Consider dried blood spot but it would take diagnosis out of realm of (near) same-day diagnosis • Plasma/serum difficult at health centres unless plasma separation is internal to the platform

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
10. Manual specimen prep (total hands-on steps after obtaining sample)	0 or 1 (no precision volume control and precision time steps)	94% (96%-68%)	Maximally 2 steps (no precision volume control and precision time steps)	86% (90%-62%)	• Minimal characteristic may be too strict • Precision volume control and time steps difficult to achieve in health centres but will likely be needed to achieve desired diagnostic and analytical sensitivities • What constitutes a step?
11. Time to result	<30 minutes	88% (92%-64%)	<90 minutes	72% (80%-52%)	• Optimal: 30 minutes is prohibitive vs others desired shorter turn-around (range: 15-60 minutes) • Minimal: 90 minutes may put burden on patients and provider workflow vs others advocated >90 minutes (range: 60-120 minutes) • May not be a key factor as long as result provided within same day
12. Specimen capacity and throughput	Multiple at a time (without batching) Random access/parallel processing	88% (92%-64%)	One at a time (any external reagents should be aliquoted for one time use)	88% (92%-64%)	• If testing done at health centres, may not need to process multiple samples at a time • How many tests would be performed per 8-hour shift? • Difficult to say due to lack of epidemiological data on HCV burden in LMIC • Throughput could be expanded through additional modules. A modular format would also allow flexibility to use the system in low- and high-volume settings
13. Biosafety + waste disposal	Closed, self-contained system; no biosafety cabinet required;	86% (90%-62%)	Closed, self-contained system; no biosafety cabinet required; unprocessed sample	86% (90%-62%)	• Could be less strict • Recycling or composting components that have contained blood and chemicals is challenging

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
	unprocessed sample transfer only; no open handling of biohazardous material; easy decontamination of the platform. Recyclable or compostable plastics for test cartridges and other material		transfer only; no open handling of biohazardous material; easy decontamination of the platform. Recyclable or compostable plastics for test cartridges and other material		• Biosafety considerations with processing whole blood
14. Instrumentation	Single integrated system ideally modular to allow module expansion of throughput	86% (90%-62%)	Single integrated system ideally modular to allow module expansion of throughput	86% (90%-62%)	• Optimal: could include ability to run other tests and/or hepatology panel cassette • Minimal: could allow for separate mini-centrifuge, results interpretation module, computer (similar to GeneXpert)
15. Power requirements	Battery operated with recharging solution (e.g. solar) and circuit protector lasting up to 8 hours.	92% (94%-66%)	Battery-operated device lasting up to 4 hours. Capable of running off standard electrical as supplied currently plus UPS (to complete current cycle); circuit protector. UPS and circuit protector must	92% (94%-66%)	• Optimal: longer battery life (e.g. 3 days of constant use) and should also be able to run off standard electricity • Minimal: may not need battery

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
			be integrated within the system.		
16. Maintenance/ calibration	Preventative maintenance at 2 years or >5,000 samples; include maintenance alert; remote or no calibration. Ability to swap out broken instruments	92% (94%-66%)	Preventative maintenance at 1 year or 1,000 samples; include maintenance alert; remote or no calibration	92% (94%-66%)	• Remote calibration may be difficult to achieve in health centre • Simple calibration with reminder to operator easier to achieve • Swap out of broken instruments difficult to achieve in practice
17. Data analysis	Integrated data analysis (no requirement for PC); exported data capable of being analysed on a separate or networked PC	80% (86%-58%)	Integrated data analysis (no requirement for PC); exported data capable of being analysed on a separate or networked PC	80% (86%-58%)	• Connectivity of these instruments will be critical for supply chain, quality assurance. Optimal would be internal connectivity
18. Result documentation/data display	Integrated results screen and ability to save and print results; USB port. On-instrument visual readout and the ability to add information (patient	88% (92%-64%)	Integrated results screen and ability to save and print results; USB port. On-instrument visual readout and the ability to add information (patient ID, operator ID, date location, etc.)	88% (92%-64%)	• Whether data is exported or manually entered is not as critical in developing countries

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
	ID, operator ID, date location, etc.)				
19. Operating temperature/ humidity/ altitude	Between +5 to +40o C at 90% humidity and at an altitude of 3000 metres	88% (92%-64%)	Between +5 to +40o C at 70% humidity and altitude of 2000 metres	80% (86%-58%)	• 40°C may be hard to achieve; perhaps 10-35°C • 2000 metres may exclude too many regions
20. Reagent kit transport	No cold chain required; tolerance of transport stress for a minimum of 72 hours at -15 to +50o C	83% (88%-60%)	No cold chain required; tolerance of transport stress for a minimum of 48 hours at -15 to + 40o C	83% (88%-60%)	• Most NAATs require enzymes, which may not be stable @ 50°C for many days
21. Reagent it storage/ stability	2 years at +5°C to +40oC at 90% humidity & transport stress (72 hours at 50oC); no cold chain required	80% (86%-58%)	18 months at +5°C to 35o C, 70% humidity & transport stress (48 hours at 50o C); no cold chain required	75% (82%-54%)	
22. Internal process quality control	Full process control, controlling for sample processing, amplification and the detection	92% (94%-66%)	Full process control, controlling for sample processing, amplification and the detection	92% (94%-66%)	
PRICING					

Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[1]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic	Collated comments from Delphi-like survey
23. Price for individual test (reagent & consumable only; at scale; ex-works)	< US$ 7	75% (82%-54%)	< US$ 15	58% (70%-42%)	• Split responses between industry requesting largely a higher cost per test and other stakeholders requesting a lower price • Trade-offs to consider (sensitivity, specimen type, healthcare implementation)
24. Capital costs for instrumentation	< US$ 500	72% (80%-52%)	< US$ 15000	63% (74%-46%)	Higher capital costs: < US$ 2000 to < 20,000

Target product profile for an HCV core antigen test for the diagnosis of active HCV infection

HCV cAg is detectable in the blood stream one to two days after HCV infection and HCV RNA appears [7], and in the "'window phase" of infection where individuals are viraemic but lack antibodies to HCV [8]. HCV cAg highly correlates with HCV RNA at RNA levels greater than 10^3 IU/ml [11], which is seen in the majority of infected patients. Moreover, during HCV treatment monitoring, decreases of cAg positively correlate with decreases of HCV RNA levels [1], indicating that HCV cAg can be a sufficient substitute for treatment monitoring, in addition to its diagnostic capabilities.

The following table indicates the results of the Delphi-like survey across the different characteristics for an HCV cAg test.

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
SCOPE					
1. Goal of test	To diagnose active HCV infection using capillary or venous whole blood specimens with the purpose of initiating treatment within the same clinical encounter (or same day). To monitor virologic response 12 weeks after treatment completion and detect virologic relapse if it occurs.	85% (92%-44%)	To diagnose active HCV infection using capillary or venous whole blood specimens with the purpose of initiating treatment within the same clinical encounter (or same day). To monitor virologic response 12 weeks after treatment completion and detect virologic relapse if it occurs.	80% (90%-42%)	• In generalized epidemics (e.g. Egypt, Mongolia), include people >50 years & those with frequent contact with health-care system • Ensure that if a test is used with same-day diagnosis, the patient does sufficiently understand the diagnosis to buy into treatment

[2] Lower and upper bounds for the ranges were calculated by assuming stakeholders who did not respond to the TPPs would have agreed with the characteristics (score of 4 or higher, upper bound) or disagreed with the characteristics (score of 3 or lower, lower bound)

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
	Note: This test is not intended for blood screening.		Note: This test is not intended for blood screening.		
2. Target population	Countries with a medium to a high seroprevalence (1.5-3.5% and >3.5%, respectively)	85% (92%-44%)	Countries with a medium prevalence to a high prevalence of HCV	80% (90%-42%)	• There are many populations with high prevalence in low prevalence countries & many may benefit from an immediate diagnosis of infection (rather than 2-step diagnosis) • Knowledge of genotype needed until we have truly pan-genotype direct-acting antiviral regimens
3. Target user of test	Health care workers with minimal training	88% (94%-46%)	Laboratory technicians with a degree of training	92% (96%-48%)	• Need well thought out definition for "minimal training" • <1 day for health-care worker (optimal) or trained laboratory technician (minimal) • Lab techs will limit ability to scale test to lower level facilities • Has to be easy to use without extensive training to facilitate scale-up • Platforms should be very easy to use such that optimally lay health-care workers or community health workers can perform the test
4. Setting for implementation (health system level)	Health centres (Level I)	92% (96%-48%)	Health centres (Level I)	92% (96%-48%)	• Include NGOS, private practice, community settings (e.g. community hall) • Would not go lower than health centres as challenge would be to have linkage to care and treatment in community testing sites.
PERFORMANCE CHARACTERISTICS					

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
5. Diagnostic sensitivity	>99%	85% (92%-44%)	>95%	88% (94%-46%)	• Clarification on comparator/reference: NAAT or current gold standard for cAg (i.e. Abbott Architect) • What trade-off in sensitivity is acceptable for increased access to diagnostic and care? Suggested minimal: 90-92%
6. Analytical sensitivity	15 IU/ml	85% (92%-44%)	1000 IU/ml	88% (94%-46%)	• 15 IU/ml unlikely with antigen testing • Suggested analytical sensitivity optimal: 500 IU/ml; minimal: 1000-3000 IU/ml • Cross-genotype consistency; Gt 3 sensitivity lower for cAg and NAAT
7. Diagnostic specificity	>99%	92% (96%-48%)	>98%	88% (94%-46%)	• Suggestion for lower specificity: 98% (optimal); 92% (minimal) • BUT: if done as a one-step diagnostic test, specificity needs to be high to avoid false positives • Clarification on comparator/reference: NAAT or current gold standard for cAg (i.e. Abbott Architect)
8. Quantitation	Not necessary	85% (92%-44%)	Not necessary	88% (94%-46%)	• Quantitation may not be needed with DAA therapies • Optimal would be quantitative. No reason to pretend it's not possible.
OPERATIONAL CHARACTERISTICS					
9. Specimen type	Capillary whole blood	100% (100%-52%)	Venous whole blood	88% (94%-46%)	• Need more data on how low (analytical sensitivity) can get with capillary whole blood • Limited studies have been done to show utility using whole blood – though it can be done, it is unclear how sensitive the test will be using whole blood

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
					• Venous blood would limit testing due to need for blood drawing facility • Should we mention dried blood spot?
10. Specimen prep + assay processing (total steps)	Integrated specimen preparation or not required	100% (100%-52%)	Limited number of steps required. No (precise) measuring needed for any step (e.g. volumes or time)	100% (100%-52%)	• Key is to reduce processing costs (human cost, additional material cost)
11. Time to result	<20 minutes, with little hands-on time	92% (96%-48%)	<1 hour, with little hands-on time	88% (94%-46%)	• Optimal could be shorter e.g. <15 minutes • Not necessary in all settings/situations to have minimal time to result <1 hour (could be faster)
12. Sample capacity	Multiple at a time	92% (96%-48%)	One specimen at a time; if instrument-based, one sample does not occupy the instrument; random access/parallel processing preferred	77% (88%-40%)	• Minimal could be less restrictive. In most health centres, daily throughput is likely not be high, in which case one specimen at a time will be fine. • Throughput and random access is a balance between time to results and affordability of the platform
13. Biosafety + waste disposal	No need for a biosafety cabinet; consumables should be able to be disposed of as biosafety waste; simple trash; recyclable or compostable	92% (96%-48%)	No need for a biosafety cabinet; consumables should be able to be disposed of as biosafety waste; simple trash; recyclable or compostable plastics/consumables;	88% (94%-46%)	• Recyclable/compostable is a challenge for components in contact with blood. Also depends on country regulation • Suggested optimal: simple trash; minimal: biosafety waste • Providing a sharps container is highly limiting and will impact shipping and cost of goods

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
	plastics/consumables; no sharps		a sharps container should be provided if a lancet is necessary		
14. Instrumentation + power requirement	Instrument free. Rechargeable battery (if required e.g. for optional reader) lasting at least 8 hours for reader	88% (94%-46%)	Small, portable or hand-held instrument (<1kg) that can operate on rechargeable battery or solar power lasting at least 4 hours (8 hours preferred)	88% (94%-46%)	• Optimal: Instrument-free may not be necessary if test implementation is at health centre; longer battery life of 3 days and external battery; no reader; consider connectivity issues, as it will be critical even with instrument-free device (thus reader is critical) • Minimal: <3 kg; weight may not be important characteristic if using at health centre, consider running hepatitis panel (Ab, CA, histology)
15. Result capture, documentation, data display	Ability to save results via separate reader	96% (98%-50%)	Ability to save results. When instrument is used, the test menu should be simple with integrated LCD screen; simple key pad or touch screen	92% (96%-48%)	• Consider connectivity issues as it will be critical even with instrument-free device (thus reader is critical) • Given some of the concerns with HIV and malaria rapid diagnostic tests, should we perhaps recommend a reader for test procedure guidance, easier interpretation and result transmission?
16. Maintenance + calibration	Disposable, no maintenance or calibration required	96% (98%-50%)	Preventative maintenance at1 year or >1000 samples; only simple tools/minimal expertise required; include maintenance alert Mean time to failure of at least 12	96% (98%-50%)	• Minimal: High complexity of managing preventive maintenance programme for numerous POC devices; Important to have built in controls. • Swapping-out of instruments is difficult; imperative that countries enter into service/maintenance contracts with suppliers at the time of instrument procurement

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
			months. Swap-out of platforms permitted. Remote or auto-calibration without the need for a computer. Preference is for no calibration required.		
17. Operating temperature and altitude	Between +5° C and +40° C at 90% humidity and up to an altitude of 3000 metres	92% (96%-48%)	Between + 5°C and +40°C at 70% humidity and up to an altitude of 2000 metres	81% (90%-42%)	• Suggested minimal: +10°C to +35°C at 0-70% relative humidity & altitude of 2000 metres
18. Internal quality control	Internal full-process positive control & negative controls	96% (98%-50%)	Internal full-process positive control	92% (96%-48%)	• Minimal could be external positive control • Rapid diagnostic tests lack both positive and negative controls. Should the quality control here follow such standard practices?
PRICING					
19. Price of individual test (reagent costs only; at scale; ex-works)	< US$ 3	85% (92%-44%)	< US$ 10	73% (86%-38%)	LOWER PRICE: • Needs to be less expensive; can be achieved through high volume • Obviously, less expensive is better. I'm just wondering where these $ amounts came from? • Price too high for low-income countries SOMEWHERE IN BETWEEN: • At scale these prices are OK. But cannot overlook the “at scale” and expect that at launch the product pricing will be at this level

Characteristic	Optimal requirements	% (range) agreeing with optimal requirements for characteristic[2]	Minimal requirements	% (range) agreeing with minimal requirements for characteristic	Collated comments from Delphi-like survey
					• Is <US$ 15 realistic as a minimum in the short term? • I am actually glad to see pricing here that might be achievable. • Not beyond US$ 10 • I'd like < US$ 5 and < US$ 10 HIGHER PRICE: • Optimal price per test may not be achievable; cost of manufacturing cAg test > US$ 3; however, optimal price should not be > US$ 5 • If cAg has comparable clinical sensitivity and faster turnaround time than NAAT, should it still be priced lower? • Need a rationale to be able to comment. If the test is cost-effective at US$ 20, this should be the goal! • A direct from blood or plasma assay attempting to achieve <1000 IU/ml in a decentralised location is a high target and may be difficult to produce for < US$ 15, therefore a higher price than US$ 15 for such an assay should be acceptable. • Molecular tests cannot be compared with serology in pricing, prices depend on country and volume. Compare with HIV global access programme, optimal is ~ US$ 10
20. Capital costs of instrumentation	< US$ 2000	69% (84%-36%)	< US$ 7000	58% (78%-30%)	• Ideally no capital cost • Clarify capital cost per module • Increase capital cost for minimum to 10K

Appendix B: Participant list

Consensus Meeting on High-priority Target Product Profiles for New HCV Diagnostics

22 April 2015

HILTON VIENNA DANUBE WATERFRONT
Vienna, Austria

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Appendix C: Abbreviations used in the report

ART	antiretroviral therapy
cAg	core antigen
CE	Conformité Européenne *(CE marking indicates compliance with EU legislation)*
DAA	direct-acting antiviral
FDA	U.S. Food and Drug Administration
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
LMIC	low- and middle-income countries
LOD	limits of detection
MSM	men who have sex with men
NAAT	nucleic acid amplification test
PCR	polymerase chain reaction
PLWH	people living with HIV
POC	point of care
PWID	people who inject drugs
RNA	ribonucleic acid
STD	sexually transmitted disease
SVR	sustained virologic response
TB	tuberculosis
TPP	target product profile
WHO	World Health Organization

Appendix D: Glossary

Analytical sensitivity and specificity: *Analytical sensitivity* represents the smallest amount of substance in a sample that can accurately be measured by an assay. *Analytical specificity* refers to the ability of an assay to measure a particular organism or substance, rather than others, in a sample. An assay's analytical sensitivity and analytical specificity are distinct from that assay's clinical diagnostic sensitivity and diagnostic specificity.

Diagnostic sensitivity and specificity: The *diagnostic sensitivity* of an assay is the percentage of persons who have a given condition who are identified by the assay as positive for the condition. *Diagnostic specificity* is the percentage of persons who do not have a given condition who are identified by the assay as negative for the condition.

One-step algorithm: Requires only one test to arrive at a diagnosis.

Two-step algorithm: Requires two tests to arrive at a diagnosis. The first test is highly sensitive but not sufficiently specific to arrive at a diagnosis and therefore requires a highly sensitive and specific test to confirm the diagnosis. A two-step algorithm is typically applied when the highly sensitive and specific test is not available where most patients present or when it is too costly.

Price of test: In this TPP, price of test is defined as the ex-works price at scale. This price does not include delivery and distribution costs. An ex-works price at market entry will likely be higher unless volume commitments can be made.

Delphi-like survey: The Delphi technique is a quantitative option aimed at generating consensus. It solicits opinions from groups in an iterative process of answering questions. After each round the responses are summarised and redistributed for discussion in the next round. Through a process of convergence involving the identification of common trends and inspection of outliers, a consensus is reached. Our process was originally outlined to use the Delphi technique. However, given that high consensus was achieved after a first round, the iterative consensus-building process was not necessary.