FIND is a global non-profit driving diagnostic innovation to combat major diseases affecting the world’s poorest populations

- WHO Collaborating Centre for Laboratory Strengthening & Diagnostic Technology Evaluation
- WHO SAGE-IVD member
- ISO-certified quality management system for IVD clinical trials

We address market failure by partnering to develop and deliver diagnostic solutions to LMICs

<table>
<thead>
<tr>
<th>ANTIMICROBIAL RESISTANCE</th>
<th>HEPATITIS C &amp; HIV</th>
<th>MALARIA &amp; FEVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEGLECTED TROPICAL DISEASES</td>
<td>PANDEMIC PREPAREDNESS</td>
<td>TUBERCULOSIS</td>
</tr>
</tbody>
</table>

Geneva (HQ)
South Africa
India
Viet Nam
Kenya
**In-vitro diagnostics (IVD)**

**What is an in-vitro diagnostic?**

- "**In-vitro diagnostics** are tests done on samples such as blood or tissue that have been taken from the human body. **In-vitro diagnostics** can detect diseases or other conditions, and can be used to monitor a person's overall health to help cure, treat, or prevent diseases"¹

**In-vitro means:**

- happening outside the body

Sensitivity and Specificity

- **Sensitivity**
  - What percentage of the time a test correctly will diagnose someone **with the** disease **who has the disease**

- **Specificity**
  - What percentage of the time a test correctly will diagnose the person **as not having** the disease **who does not have the disease**

Regulatory bodies governing IVD quality
Why are regulatory authorities needed?

- There are several components that go into ensuring that the diagnostic being used is giving correct results.
- For today’s session will focus on one aspect; stringent regulatory authority (SRA)/WHO Prequalification.
- SRA is a regulatory body that ensures that a diagnostic is quality assured;
  - basically that the diagnostic does what it says it will do; it will correctly identify a specific disease in the sensitivity and specificity ranges as stated by the manufacturer.
  - that the manufacturing facility and process is uniform so as to produce diagnostics of a consistent standard.
Different types of regulatory authorities

Global

- WHO Prequalification (often times called WHO “PQ”)
- Expert Review Panel for Diagnostics (ERPD)

Country/region specific (non-exhaustive)

- Australia, Therapeutic Goods Administration
- European Union, European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs
- Japan, Pharmaceuticals and Medical Devices Agency and the Ministry of Health, Labour and Welfare
- United States of America, US Food and Drug Administration
WHO Prequalification and Expert Review Pannel

- WHO Prequalification (often times called WHO “PQ”)
  
  **Why it is important:** helps ensure quality of a diagnostic and if a diagnostic has WHO PQ then that specific make/model can be procured through UN and Global Fund

  Source: [https://www.who.int/topics/prequalification/en/](https://www.who.int/topics/prequalification/en/)

  Where you can look up what diagnostics are currently WHO PQ:
  [https://www.who.int/diagnostics_laboratory/evaluations/191029_prequalified_product_list.pdf?ua=1](https://www.who.int/diagnostics_laboratory/evaluations/191029_prequalified_product_list.pdf?ua=1)

  Additional information on WHO Prequalification: [https://www.who.int/diagnostics_laboratory/evaluations/en/](https://www.who.int/diagnostics_laboratory/evaluations/en/)

- Expert Review Panel for diagnostics (ERPD)
  
  **Why it is important:** Hosted by WHO, the expert review panel consists of independent experts that review diagnostics that have not yet gone through/are in the process of going through WHO PQ or SRA review. Diagnostics that are reviewed to be of a quality standard are eligible to be procured using Global Fund funds.


  Where you can look up what diagnostics are currently have ERPD approval:
  [https://www.theglobalfund.org/media/5878/psm_productshiv-who_list_en.pdf](https://www.theglobalfund.org/media/5878/psm_productshiv-who_list_en.pdf)
Context is important

Each country has its own landscape when it comes to diagnostic regulations:

- Some require in-country studies to be done on the tests.
- Others accept tests to be registered if already WHO PQ/FDA/CE or equivalent.
WHO HCV testing algorithm
Hepatitis C
Course of illness

- Cure: 20%
- Acute infection: 80%
- Chronic inflammation of the liver
- Fibrosis
- Cirrhosis of the liver (15-20%)
- Cancer of the liver (1-4% per year)
WHO HCV Testing guidelines; https://apps.who.int/iris/bitstream/handle/10665/254621/9789241549981-eng.pdf?sequence=1

1. **SEROLOGICAL TESTING**
   - **ANTI-HCV ANTIBODY**
     - Single RDT or laboratory-based immunoassay
     - Anti-HCV + (reactive) Report positive
     - Anti-HCV – (non-reactive) Report negative

2. **CONFIRMATION OF HEPATIC INFECTION**
   - **HCV RNA NUCLEIC ACID TEST (NAT)** (qualitative or quantitative) or HCV core antigen (CAg)
     - HCV RNA test or CAg + Report detected (with viral load if available)
     - HCV RNA test or CAg - Report not detected

3. **TREATMENT ASSESSMENT**
   - **ASSESSMENT OF STAGE OF LIVER DISEASE** (using clinical criteria and non-invasive tests (NITs), i.e. APRI score > 2 or based on TE)
   - **OTHER CONSIDERATIONS FOR TREATMENT** (e.g. comorbidities, HCV genotyping, pregnancy and potential drug-drug interactions)

4. **MONITORING**
   - **ASSESSMENT OF CURE** (sustained virological response (SVR) at 12 weeks (i.e. SVR 12) after the end of treatment)
   - **HCV RNA NAT** (qualitative or quantitative)

   - **DETECTION OF HCC** (in persons with cirrhosis (every 6 months))

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1. Single test for ‘screening’

2. Prompt blood draw for test to see if the person has viremia

3. Determine liver staging using non-invasive tests

4. Treat all with pangenotypic regimens

One test of cure at 12 weeks after completion of treatment
Serological testing for HCV
Serological tests (also called serological assays), tests that screen for HCV

**Serological assays:**
- Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary/venous whole blood and oral fluid. These include rapid diagnostic tests (RDTs), and laboratory-based immunoassays, e.g. enzyme immunoassays (EIAs)

**Rapid diagnostic test (RDT)**
- Immunoassays that detect antigen or antibodies and can give a result in less than 30 minutes.

**Enzyme immunoassay (EIA)**
- Immunoassays that detect antigen or antibodies
Screening for HCV

Centralized settings
- Settings: well-equipped lab
- Operator: qualified lab technician
- Specimen type: plasma, serum
- Turnaround time: >2 hours

Dried Blood Spots
- Currently off-label; needs field validation

Decentralized settings
- Settings: primary facility
- Operator: trained healthcare worker
- Specimen type: capillary blood, oral fluid
- Turnaround time: 5-20 min

EIA
CIA
RDT (blood-based)
RDT (oral fluid-based)
## Hepatitis C antibody Rapid Diagnostic Test (RDT) that are WHO PQ’d

<table>
<thead>
<tr>
<th>Product name</th>
<th>Manufacturer</th>
<th>Performance*</th>
<th>Sample type</th>
<th>WHO PQ?</th>
<th>Stringent Regulatory Authority</th>
<th>List (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Anti-HCV Test</td>
<td>InTec PRODUCTS, INC</td>
<td>Sens: 99.2% Spec: 99.1% in mono-infected&lt;br&gt;Sens: 91.7%&lt;br&gt;Spec: 99.2% in HIV-co-infected</td>
<td>Serum/Plasma/Whole Blood</td>
<td>Yes</td>
<td>RoW</td>
<td>1.6 to 2.4</td>
</tr>
<tr>
<td>SD BIOLINE HCV</td>
<td>Standard Diagnostics, Inc.</td>
<td>Sens: 99.5% Spec: 99.6% in mono-infected&lt;br&gt;Sens: 88.6%&lt;br&gt;Spec: 99.7% in HIV-co-infected</td>
<td>Serum/Plasma/Whole Blood</td>
<td>Yes</td>
<td>RoW</td>
<td>1 to 2.4</td>
</tr>
<tr>
<td>OraQuick® HCV Rapid Antibody Test Kit</td>
<td>OraSure Technologies, Inc.</td>
<td>Sens: 99.5% Spec: 99.6% in mono-infected&lt;br&gt;Sens: 89.4%&lt;br&gt;Spec: 99.4% in HIV-co-infected</td>
<td>Serum/Plasma/Whole Blood/Body Fluids</td>
<td>Yes</td>
<td>CE mark</td>
<td>8 (MSF Access price)&lt;br&gt;14 (on US market)</td>
</tr>
<tr>
<td>First Response® HCV Card Test</td>
<td>Premier Medical Corporation Pvt. Ltd., Nani Daman, India</td>
<td>Sens: 99.5% Spec: 100% in mono-infected&lt;br&gt;Sens: 90.5%&lt;br&gt;Spec: 99.7% in HIV-co-infected</td>
<td>Serum/Plasma/Whole Blood</td>
<td>No-ERPDP</td>
<td>CE mark</td>
<td>.60 to 1</td>
</tr>
</tbody>
</table>

* FIND 2019, publication forthcoming
## HCV EIA, WHO PQ’d

<table>
<thead>
<tr>
<th>Product name</th>
<th>Manufacturer</th>
<th>Sample type</th>
<th>WHO PQ?</th>
<th>Stringent Regulatory Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCHITECT HCV Ag assay**</td>
<td>Denka Seiken Co., LTD, Kagamida Factory</td>
<td>Serum/Plasma</td>
<td>Yes</td>
<td>CE mark</td>
</tr>
<tr>
<td>INNOTEST HCV Ab IV</td>
<td>Fujirebio Europe NV</td>
<td>Serum/Plasma</td>
<td>Yes</td>
<td>CE mark</td>
</tr>
<tr>
<td>INNO-LIA HCV Score</td>
<td>Fujirebio Europe NV</td>
<td>Serum/Plasma</td>
<td>Yes</td>
<td>CE mark</td>
</tr>
<tr>
<td>Murex anti-HCV (version 4.0)</td>
<td>DiaSorin South Africa (Pty) Ltd.</td>
<td>Serum/Plasma</td>
<td>Yes</td>
<td>RoW</td>
</tr>
<tr>
<td>*Bioelisa HCV 4.0</td>
<td>Biokit S.A.</td>
<td>Serum/Plasma</td>
<td>Yes</td>
<td>CE mark</td>
</tr>
</tbody>
</table>

** ARCHITECT HCV Ag assay can be used for confirmation of viraemia, the other tests on this list can be used to determine presence of HCV antibodies
Self-testing (serology)
Currently available data on HCV self-testing is very limited

- One published report investigates acceptability of HCV self-testing among persons who inject drugs in the UK (Guise et al. 2018).
  - The study showed potential acceptability but also revealed multiple concerns associated with self-testing, primarily poor access to confirmatory testing and care.

- Another published study by Kimble and colleagues (2019) assessed the performance of OraQuick® HCV Rapid Antibody Test (Orasure Technologies, Inc., Bethlehem, PA) on oral fluid specimens when used by patients for self-testing.
  - The study included 95 participants and showed 88.4% sensitivity and 100% specificity of the test when used for self-testing compared to manufacturer-reported 98.1% and 99.6% when used by a professional healthcare provider (http://orc.orasure.com/default.aspx?pageid=1475).
  - Participants found testing procedure easy but reported some difficulties in interpreting test results. It is important to note that in this study graphical instructions for use were not provided by a test manufacturer but developed by the study team.
**HCV self-testing: pilot feasibility study**

- Objectives: determine acceptability and usability of HCV self-testing
- Several countries in different geographic regions:

<table>
<thead>
<tr>
<th>Country</th>
<th>Settings</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egypt</td>
<td>District hospital (ALPC)</td>
<td>General population</td>
<td>Completed</td>
</tr>
<tr>
<td>China</td>
<td>CBO</td>
<td>MSM</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Kenya</td>
<td>CBO</td>
<td>PWID</td>
<td>In preparation</td>
</tr>
<tr>
<td>Georgia</td>
<td>Harm reduction centers, PreP clinics</td>
<td>PWID, MSM</td>
<td>In preparation</td>
</tr>
<tr>
<td>Vietnam</td>
<td>CBO</td>
<td>PWID, MSM</td>
<td>In preparation</td>
</tr>
</tbody>
</table>

- 100-200 participants per site
- OraSure HCV Rapid diagnostic test adapted by the manufacturer for self-testing (research use only)
Combo testing (serology)
6.4.2 Integrating the diagnosis of hepatitis with diagnostic platforms and laboratory services used for other infections

Combination integrated multidisease serological tests
The use of combination integrated blood- or oral-based multidisease assays allow for integrated testing of HIV, HBV and HCV. Using a single specimen improves the efficiency of testing programmes, especially in populations with a high prevalence of HIV/HCV or HBV/HCV coinfection. While not yet fully validated, preliminary results of these combination assays appear promising (160).
## Multiplex serology testing (combo tests)

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Detection</th>
<th>Regulatory status (SRA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detect 3 HIV/HCV/HBV combo kit</td>
<td>Artron Laboratories (Canada)</td>
<td>X X X</td>
<td>CE (plasma, serum)</td>
</tr>
<tr>
<td>Triplex HIV, HCV, HBsAg</td>
<td>Biosynex (France)</td>
<td>X X X</td>
<td>NA</td>
</tr>
<tr>
<td>Hep B, Hep C, HIV Combination Rapid Test</td>
<td>Maternova (US)</td>
<td>X X X</td>
<td>NA</td>
</tr>
<tr>
<td>Multiplo HBc/HIV/HCV</td>
<td>MedMira (Canada)</td>
<td>X X X</td>
<td>RRUO</td>
</tr>
<tr>
<td>HBsAg/HCV Ab Rapid Test</td>
<td>Spectrum Diagnostics (Egypt)</td>
<td>X X</td>
<td>NA</td>
</tr>
<tr>
<td>Rapid HBsAg/HCV/HIV/Syphlis Combo</td>
<td>Euro Genomas (Lithuania)</td>
<td>X X X</td>
<td>CE</td>
</tr>
<tr>
<td>OnSite HBsAg/HCV Ab Rapid Test</td>
<td>CTK Biotech (US)</td>
<td>X X</td>
<td>NA</td>
</tr>
<tr>
<td>COMBIQUIC HIV/HCV</td>
<td>Qualpro Diagnostics (India)</td>
<td>X X</td>
<td>NA</td>
</tr>
<tr>
<td>TriQuick HIV/HCV/HCV</td>
<td>Genlantis Diagnostics</td>
<td>X X X</td>
<td>NA</td>
</tr>
</tbody>
</table>

Field validation is needed to assess diagnostic accuracy of these tests
Diagnosis of hepatitis C virus: confirmation of active infection
Prompt or reflex HCV RNA or HCV core Ag testing
Confirmation of viremia for HCV

Centralized settings
- HCV RNA
- HCV core antigen test

Settings: well-equipped lab
Operator: qualified lab technician
Specimen type: plasma, serum
Turnaround time: >5 hours

Dried Blood Spots
Currently off-label; needs field validation

Decentralized settings
- HCV RNA

Settings: district hospitals
Operator: trained healthcare worker
Specimen type: capillary blood/plasma
Turnaround time: 60-90 min

In development:
- HCV core antigen RDT

Currently off-label; needs field validation
Each conventional molecular instrument possesses unique features, which need to be considered when defining the optimal device mix within a Lab Network.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Cobas 4800-6800-8800</th>
<th>CAP/CTM 96</th>
<th>m2000sp</th>
<th>Panther</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplier</td>
<td>Roche</td>
<td>Roche</td>
<td>Abbott</td>
<td>Hologic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assays</th>
<th>HIV (EID;VL); HPV; HCV; HBV; TB</th>
<th>HIV (EID;VL); HCV; HBV; TB</th>
<th>HIV (EID;VL); TB; HPV; HCV</th>
<th>HIV (EID; VL); HPV; HCV; HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV sample types</td>
<td>DBS; Plasma; PSC (VL)</td>
<td>DBS; Plasma</td>
<td>DBS; Plasma</td>
<td>DBS (VL); Plasma</td>
</tr>
<tr>
<td>HCV sample types</td>
<td>Plasma (PSC and DBS in the pipeline)</td>
<td>Plasma</td>
<td>Serum; Plasma (DBS in the pipeline)</td>
<td>Serum; Plasma (DBS in the pipeline)</td>
</tr>
</tbody>
</table>

**Infrastructure Requirements**

| Space requirements | 1.8 m² - 5.5 m², Fixed | 3 m², Fixed | 3.15. m², Fixed | 1 m², Moveable |
| Human resources    | 1-2 FTEs/machine        | 1-2 FTEs/machine | 1-2 FTEs/machine | 1 FTE/<4 machines |

**Workflow Requirements**

<table>
<thead>
<tr>
<th>Workflow</th>
<th>Batch</th>
<th>Batch</th>
<th>Batch</th>
<th>Random access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throughput (8hr)</td>
<td>192-960</td>
<td>168</td>
<td>96</td>
<td>320</td>
</tr>
<tr>
<td>Time to first result (hr)</td>
<td>&lt; 3.5</td>
<td>~5.5</td>
<td>~5.5</td>
<td>&lt; 3.5</td>
</tr>
</tbody>
</table>
Dried blood spot (DBS)
Validation of DBS sampling

DBS sampling for HCV RNA test

Aim: provide HCV diagnostics in the settings with no access to laboratory infrastructure

Concept:

FIND study: multicenter diagnostics accuracy study to obtain evidence of the performance of HCV RNA tests from DBS/PSC (with the intention of data to be included to companies’ regulatory dossiers)
- real-life conditions: RT transport and storage of DBS and PSC samples
- DBS and PSC processing using manufacturers’ protocols
  - Abbott M2000
  - Roche cobas® 4800 and 6800 (PSC and DBS)
  - Hologic Panther

Study sites:
- Georgia
- Cameroon
- Greece
- Rwanda
- Australia (NRL — central testing)

Sample size: 415 HCV RNA positives, 415 HCV RNA negatives
Timeline: Q1 2019 — Q3 2019

A project funded by

Unitaid
Innovation in Global Health
Point of Care (POC) and near POC
### Near-POC HCV RNA assays available on the market

<table>
<thead>
<tr>
<th>PLATFORM</th>
<th>Xpert HCV VL assay</th>
<th>Xpert HCV Fingerstick VL assay</th>
<th>GeneDrive HCV ID assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Xpert HCV VL assay" /></td>
<td><img src="image2" alt="Xpert HCV Fingerstick VL assay" /></td>
<td><img src="image3" alt="GeneDrive HCV ID assay" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>Plasma</th>
<th>Capillary blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSITIVITY</td>
<td>99%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>SPECIFICITY</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SAMPLE PREPARATION</td>
<td>Integrated</td>
<td>Integrated</td>
<td>Off-board (several pipetting steps)</td>
</tr>
<tr>
<td>TIME TO RESULT</td>
<td>110 min</td>
<td>60 min</td>
<td>~120 min</td>
</tr>
<tr>
<td>REGULATORY STATUS</td>
<td>CE-IVD, WHO PQ</td>
<td>CE-IVD</td>
<td>CE-IVD</td>
</tr>
<tr>
<td>POWER SUPPLY</td>
<td>Need electricity supply</td>
<td></td>
<td>Need electricity supply</td>
</tr>
<tr>
<td>DATA ANALYSIS</td>
<td>PC</td>
<td></td>
<td>Integrated</td>
</tr>
<tr>
<td>TEST MENU</td>
<td>TB, HIV, HBV and many others</td>
<td></td>
<td>TB in development</td>
</tr>
<tr>
<td>TEST COST</td>
<td>US$ 14.95 ex works</td>
<td></td>
<td>Not disclosed</td>
</tr>
<tr>
<td>INSTRUMENT COST</td>
<td>US$ 17,500</td>
<td></td>
<td>Not disclosed</td>
</tr>
</tbody>
</table>
cAg RDT
HCV core Ag RDT concept

Main technical challenge: high analytical sensitivity requirements unlikely to be met in RDT format

HCV core Ag RDT will have 75-85% clinical sensitivity, but impact will likely outweigh suboptimal sensitivity
Liver staging
Assess and triage; Stage liver disease using NITs (APRI, FIB4, TE)
### Existing liver staging options

<table>
<thead>
<tr>
<th>Biochem</th>
<th>aspartate aminotransferase to platelet ratio index (APRI)</th>
<th>Uses blood test for a blood test to measure your aspartate aminotransferase (AST) and a platelet count</th>
<th>Machines needed to conduct the blood tests can usually be found at level 1 health centers. Is relatively inexpensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB4</td>
<td>Is a formula based on several laboratory tests: ( \frac{\text{Age} \times \text{AST}}{\text{Plts} \times \sqrt{\text{ALT}}} )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibroscan</th>
<th>Machine which can provide liver staging results</th>
<th>Machine is expensive</th>
<th>Requires trained technician</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Is not widely available in all countries/contexts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Can be used to provide liver staging results</th>
<th>While often machines are already in place for other services requires trained technician</th>
<th>Wait times for ultrasound appointment can be long as other patient types may be prioritized (pregnant women)</th>
</tr>
</thead>
</table>
One test of cure at 12 weeks after completion of treatment
Thank you!

**We believe**
Simple, rapid, robust and affordable diagnostic solutions bring game-changing possibilities above and beyond their immediate benefit.

**We believe**
Our work can spark real progress in the health of lower and middle income countries and their populations.

**We believe**
With improved health comes greater hope: individuals empowered to support their families, revive businesses, and thrive in school.