Stop TB Partnership

New Diagnostics Working Group

Annual Meeting 2014
Barcelona, 29 October 2014

Daniela Cirillo San Raffaele Scientific Institute
Co-Chair, NDWG
New Diagnostics Working Group

Fostering development of new diagnostic tools for TB

Vision
High quality diagnosis of tuberculosis and drug resistance is available for all people in all settings.

Mission
Foster development and evaluation of new diagnostics for tuberculosis by serving as a coordination, communication and advocacy platform for all stakeholders in TB diagnostic research and development.
Connecting partners

The NDWG serves as a forum for stakeholders, provides a coordination and communication platform for effective collaboration and develops technical resources towards delivery of new TB diagnostics, by

1. Assuring coordination between partners
2. Establishing mechanisms for strategic information and knowledge sharing
3. Identifying and promoting promising innovation
4. Advocating for new TB diagnostics, for increased funding for TB diagnostic R&D and for evidence-based decision making to drive WHO policy
Five priority actions to address the MDR-TB crisis

1. Prevent the development of drug resistance through high quality treatment of drug-susceptible TB

2. Expand rapid testing and detection of drug-resistant TB cases
   
   By 2020 DST UNIVERSAL COVERAGE

3. Provide immediate access to effective treatment and proper care

4. Prevent transmission through infection control

   LARGE SCALE IMPLEMENTATION OF CULTURE DST LABORATORIES

5. Increase political commitment with financing

   LARGE SCALE IMPLEMENTATION OF MOLECULAR DIAGNOSTICS
Main differences

**CULTURE BASED DST**
- Culture based
- Evaluate the growth of bacteria (or a proportion of the overall inoculum) in the presence of an *established* concentration of drug

**MOLECULAR BASED DST**
- Detects mutations in genes relevant for the mechanism of action:
  - Synonymous mutations
  - Mutations not interfering with the mechanism of action of the drug
  - Mutations highly interfering with the DRUG pathway

Class of drug | Single drug
The current challenge

To develop a process by which mutations in MTB can in a systematic and transparent manner be shown to have adequate objective evidence to support a claim indicative of the mutation either causing or being associated with resistance to a known and identified drug and/or drug class.
Link between sequencing data (Sanger? NGS) high quality phenotypic (gold standard??) data and clinical outcome on large sets of DRUG RESISTANT and DRUG SENSITIVE strains.

Use of phenotypic tests as “absolute” standard and the poor quality of some results has biased our comparative evaluation of molecular tools.

Analysis on extremely large data sets (>50,000 genomes) can compensate for phenotypic DST errors.

Molecular Diagnostic Pipeline

<table>
<thead>
<tr>
<th>High complexity assays</th>
<th>Moderate complexity assays</th>
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<tbody>
<tr>
<td>Hain GenoType MTBDRplus</td>
<td>Cepheid Xpert® MTB/RIF</td>
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<tr>
<td>Roche Cobas</td>
<td>iCubate</td>
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<tr>
<td>Abbott TBMDx</td>
<td>NanoBioSys LabChip G2-3</td>
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<tr>
<td>Zeesan MolPro®</td>
<td>Eiken TBLAMP™</td>
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| Hain GenoType MTBDRplus | Cepheid Xpert Ultra 
Xtend-XDR |
| Veredus Laboratories VereMTB™ | Northwestern GHT/Quidel |
| YD REBA MTB-XDR REBA MTB-Rita | Cepheid Enzyme ML® MDR TB |
| Hain LATE PCR Lights on iLights off MTB-PZA | Ustar MTB |
| BD BD Max | Akkoni MDR-TB |

FIND

<table>
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<tr>
<th>WHO-endorsed</th>
<th>Limited commercial availability</th>
<th>In development</th>
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<td></td>
<td>2015</td>
<td>2016</td>
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Aligning diagnostics with treatment to provide the best available therapeutic options

Joining forces
Sharing data
Avoid duplication
Sequencing to directly inform patient care

Enhance sequencing for surveillance and DRS

Inform developers of molecular tests

Guide new drugs development and early detection of resistance mechanisms

Data evaluation

Expert consensus process

OPEN ACCESS DATABASE

Surveillance data sets

Research data sets

Geographically representative data sets
The Process

- **Consensus based (HIV-1 resistance database for TruGene)**
  - Expert Panel
    - Geographic diversity
    - Representative areas of expertise
  - Develop quality metrics and requirements for
    - Data inclusion for the database for mining
      - Genotypic
      - Phenotypic
      - Metadata
    - Data weighting system
    - Validation algorithm/process for association to resistance
      - Validity criteria
      - Acceptance criteria
    - WHO endorsement of the ‘validated’ resistance mutation
The Panel

• Expert Panel
  – Geographic diversity
    • Five (5) core members
    • Up-to ten (10) co-opted members
  – Representative areas of expertise
  – Initially meetings will be up to 4 times per year
  – Supervised by FIND and NDWG (the persons acting as coordinating chairs will have no voting rights)
    • Coordinate dates of meetings
    • Setup and run the meeting
    • Prep data packages
Two Step Approach

**FIRST Step**

- What do we know now?
- TPP development
- Identification of high confidence markers of resistance
- Inform developers of molecular tests

**SECOND Step**

- Enhance sequencing for surveillance
  - Country capacity strengthening
  - Integration of data in database
- Sequencing to directly inform patient care
  - Optimization of sample preparation for sequencing
  - Development of more automated solutions
The role of the NDWG

To provide the coordination and communication with stakeholders
In partnership with lead experts in the field

– Ensure the quality of the data
– Drive the development of criteria for the validation of mutations
– Create a ‘living’ list of mutations
– Define algorithms for the interpretation of genotypic data and their correlation with clinically relevant resistance in *M. tuberculosis*.
TB Drug Resistance Data Sharing Platform

• CPTR - a strong partner
  – With established capabilities in management of large amounts of data
  – With linkage to drug development
NDWG Core Group

Co-Chairs
Dr. Catharina Boehme, FIND
Dr. Daniela Cirillo, San Raffaele Research Institute

Core Group Members (and constituency)
• Dr. Martina Casenghi, MSF (NGOs)
• Dr. Anne Detjen, IUATLD/TB TREAT, USA (IUATLD)
• Dr. Christopher Gilpin, WHO Global TB Programme (WHO)
• Dr. Rumina Hasan, Aga Kahn University, (GLI)
• Philippe Jacon, Cepheid (Industry)
• Dr. Stefan Niemann, Borstel Research Institute (Academia)
• Dr. Mark Perkins, FIND (Diagnostic Developers)
• Dr. John Ridderhof, CDC Atlanta, (CDC)
• Dr. Charles Sandy, National TB Program, Zimbabwe (NTP)

Subgroups and Coordinators
Point-of-Care Diagnostics Dr. Ruth McNerney (LSHTM)
Diagnosis of Latent TB Infection Dr. Keertan Dheda (University of Cape Town) and Dr. Philip Hill (University of Otago) (jointly)
Evidence Synthesis and Policy Dr. Karen Steingart (Cochrane Infectious Diseases Group)
Childhood TB and Diagnostics Dr. Anneke Hesseling (Stellenbosch University)
Community, Poverty and Advocacy Mayowa Joel (Communication for Development)

Secretariat Alessandra Varga, FIND
Thank you

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<tr>
<th>WHO</th>
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<th>NDWG</th>
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<tr>
<td>CPTR</td>
<td>Catharina Boehme</td>
<td>Alessandra Varga</td>
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<td>C-PATH</td>
<td>Claudia Denkinger</td>
<td>Stefan Niemann</td>
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<td>BMGF</td>
<td>David Dolinger</td>
<td>John Ridderhof</td>
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http://www.stoptb.org/wg/new_diagnostics/