Data Sharing to Improve Management of Drug Resistant TB

Plans for Data Evaluation and Validation

David L. Dolinger, Ph.D.

28 October 2014
Statement of the Challenge

**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
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
Goals

- Evaluate existing and prospective data to determine clinically valid resistance associated mutations

- Consensus definitions around of drug sensitive and resistance

Publication

- Process validation of the validation process - transparency
- Periodic publication of the up-dated mutation panel
- Validity and Acceptance criteria for a mutation to be associated with resistance
  - Published and unpublished supporting data
  - Statistical/quality score for the mutation
<table>
<thead>
<tr>
<th>Risk/Hazard</th>
<th>Severity</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unwillingness of researchers and countries to share sequencing and meta-data</td>
<td>Critical</td>
<td>Leverage NDWG and the Resistance Mutation Validation Expert Panel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion of researchers from geographically diverse regions (incl. China and India) on the Resistance Mutation Validation Expert Panel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Utilize additional key opinion leaders to initiate discussion with Ministries of Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provide additional tools and algorithms that can be utilized by researchers for data mining</td>
</tr>
<tr>
<td>Diversity of data quality and variety</td>
<td>Critical</td>
<td>Develop quality standards</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Work with developers to assure that all</td>
</tr>
<tr>
<td>Limited data connecting mutations to phenotype and clinical outcomes</td>
<td>Critical</td>
<td>Inform and drive further research investments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Establish a tiered, statistically-driven interpretation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>taking into account the certainty of knowledge</td>
</tr>
</tbody>
</table>
Summary

- **Precedence for the approach**
  - HIV-1 (FDA cleared TRUGENE Genotyping Kit)

- **Buy in**
  - Internal
  - External

- **Focus**
  - Appropriate documentation for informed decisions
    - Published
    - Mined

- **Dedication**
  - To the ultimate outcome – the patient
천 리 길도 한 걸음부터
“The journey of a thousand ri begins with a single step.”
Thank you

FIND
Catharina Boehme
Peter Kaspar
Claudia Denkinger

NDWG
Daniela Cirillo
Alessandra Varga
Others

CPTR
C-PATH
BMGF
Definitions

- **Quality Control** – part of quality management focused on fulfilling quality requirements; In health care testing, the set of procedures designed to monitor the test method and the results to ensure appropriate test system performance.

- **Quality Assurance** – part of quality management focused on providing confidence that quality requirements will be fulfilled.

- **Quality Assessment** – systematic process of collecting and analyzing data to determine the current, historical, or projected status of an organization, person, assay or project.

- **Validation** – confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled; Confirmation by examination and provision of objective evidence that specified requirements for a specific intended use can be consistently fulfilled; Establishing and documenting evidence, which provides a high degree of assurance that a device will consistently produce a result or product meeting its predetermined specifications.

- **Acceptance Criteria** – a defined set of conditions that must be met to establish the performance of a solution (system, platform, test, data).

- **Validity Criteria** – the degree to which the inference drawn from a test is warranted when account is taken of the test method, the representativeness of the test sample, and the nature of the population from which it is drawn; two varieties exist – internal and eternal.