CRITICAL PATH INSTITUTE

CPTR 2017 Workshop: Day 3 – March 22, 2017

The 8th Annual CPTR Initiative Workshop drew more than 150 participants to Washington, D.C. to learn and share information critical to the rapid advancement of new TB combination therapies, drug susceptibility tests (DST), and the tools and models necessary to develop and implement them. Participants represented a diverse group of global stakeholders, including product developers, regulators, health systems workers, and TB survivors and patient advocates. Detailed summaries and content from Day 3 of the 2017 CPTR Workshop is provided below.

AGENDA

8:15 – 8:30 am	**Welcoming Remarks** *Jim Gallarda (Bill & Melinda Gates Foundation)*
8:30 – 9:00 am	**Keynote Address: Learning from the Impact of the Drug-Diagnostic Development Strategy in Oncology** *Jan Trost Jorgensen (Dx-Rx Institute)*
Roundtable Discussion on Patient Centric Solutions – In-Country Perspectives ***Moderator: Madhukar Pai (McGill University)***	
9:00 – 9:15 am	**Keynote Address: Learning from the Impact of the Drug-Diagnostic Development Strategy in Oncology** *Diego Silva (Simon Fraser University)*
9:15 – 9:30 am	**From Tools to Patient-Centric Solutions** *Madhukar Pai (McGill University)*

9:30 – 10:30 am	**Panel Discussion** *Moderator: Madhukar Pai (McGill University)* *Panelists: Diego Silva (Simon Fraser University), Sunil Khaparde (National TB Programme, India), Betina Durovni (Fiocruz), Phumeza Tisile (TB Proof), Beatrice Mutayoba (National TB and Leprosy Programme, Tanzania)*
10:30 – 10:45 am	**Break**

Collaborations for Advancing Drug Susceptibility Test Development

Moderator: Tim Rodwell (FIND)

10:45 – 10:55 am	**Session Introduction** *Tim Rodwell (FIND)*
10:55 – 11:10 am	**Prediction of Drug Resistance Using Genotypic Data: An Argument for Machine Learning** *Maha Farhat (Harvard University)*
11:10 – 11:25 am	**A Standardized System for Grading Mutations in Mycobacterium tuberculosis for Association with Drug Resistance** *Paolo Miotto (San Raffaele Scientific Institute)*
11:25 – 11:40 am	**What are we trying to say here? Standardizing Next Generation Sequencing Reports for TB** *Jeff Tornheim (Johns Hopkins University)*
11:40 – 11:55 am	**The Genomic Epidemiology Ontology and Proof Sheet Application** *Damion Dooley (University of British Columbia)*
11:55 – 12:30 pm	**Panel Discussion** *Moderator: Tim Rodwell (FIND)* *Panelists: Maha Farhat (Harvard University), Paolo Miotto (San Raffaele Scientific Institute), Jeff Tornheim (Johns Hopkins University), Damion Dooley (University of British Columbia)*

12:30 – 1:30 pm	**Lunch**
Topical Breakout Sessions	
1:30 – 2:45 pm	**Demo and Training – Hands-on tutorial on the Interactive Tool for an Optimal Positioning of Time-to-Positivity (TTP) Results in Patients with TB***Chairs: Klaus Romero (Critical Path Institute) and Nastya Kassir (Certara)* **Addressing Interoperability Between Data Platforms** *Chair: Amanda Borens (Critical Path Institute)* **Fostering Industry and Regulatory Interactions to Advance Next Generation Sequencing for TB Diagnostics** *Chair: Steven Gitterman (Food and Drug Administration)*
2:45 – 3:00 pm	**Break**
Innovative Partnerships to Advance Data Sharing Across Databases ***Moderator: Marco Schito (Critical Path Institute)***	
3:00 – 3:05 pm	**Session Introduction** *Marco Schito (Critical Path Institute)*
3:05 – 3:45 pm	**Brief Updates on Database Efforts** *Maha Farhat (Harvard University)* *Raja Mazumder (George Washington University)* *Damion Dooley (University of British Columbia)* *Alison Yao (National Institute of Allergy and Infectious Diseases)* *Patrick Phillips (UK Medical Research Council)* **Panel Discussion**
3:45 pm	**Adjourn**

Welcoming Remarks

Jim Gallarda (Bill & Melinda Gates Foundation)

Jim Gallarda opened the day's agenda by reminding participants of the importance of collaboration and that silos often act as the largest impediments to progress in global health.

- Video

Keynote Address: Learning from the Impact of the Drug-Diagnostic Development Strategy in Oncology

Jan Trost Jorgensen (Dx-Rx Institute)

Jan Trost Jorgensen addressed the similarities and differences in drug and diagnostic development strategies between cancer and tuberculosis. The heterogeneity of the disease must inform the approaches to tools development. Jorgensen noted that the successes of drug development in oncology are strongly related to development and use of companion diagnostics. Additionally, such coordination reduces the overall cost of drug development as it leads to less failure and increased speed and efficiency. This model is highly applicable to the challenges facing TB drug and diagnostic development and deployment.

- Video
- Video (Q&A)
- Presentation

Roundtable Discussion on Patient Centric Solutions – In-Country Perspectives

Moderator: Madhukar Pai (McGill University)

Ethics Considerations in the Development and Implementation of TB Diagnostics

Diego Silva (Simon Fraser University)

Diego Silva stressed that the existence of diagnostics is alone insufficient. They must be used properly, and further, even when used properly, they must lead patients to available and effective care. Silva articulated the differences between clinical health and public heath goals as they relate to diagnosis – there is no direct health benefit to accurate diagnosis if that person can't be cured. This serves as a reminder to approach product development with the end, and end-user, in mind.
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From Tools to Patient-Centric Solutions

Madhukar Pai (McGill University)

Madhukar Pai presented a detailed map of patient care, showing how patients struggle to access new tools. Pai reiterated that health systems are not equipped and prepared to effectively diagnose TB outside the National Treatment Programs. The cascade of care in TB in India reveals where people drop off and lose access to care; diagnosis is the biggest problem. Pai presented a similar analysis for MDR-TB patients in South Africa. Many opportunities to fall off the path to care exist, so solutions are required across the entire spectrum of care. Pai noted that it is encouraging that use of GeneXpert is trending in the right direction, yet countries still seem to be under-utilizing tools they have bought into and invested in.

- Video
- Presentation

Panel Discussion

Moderator: Madhukar Pai (McGill University)

Panelists: Diego Silva (Simon Fraser University), Sunil Khaparde (National TB Programme, India), Betina Durovni (Fiocruz), Phumeza Tisile (TB Proof), Beatrice Mutayoba (National TB and Leprosy Programme, Tanzania)

- Video

Collaborations for Advancing Drug Susceptibility Test Development

Moderator: Tim Rodwell (FIND)

Session Introduction

Tim Rodwell (FIND)

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Prediction of Drug Resistance Using Genotypic Data: An Argument for Machine Learning

Maha Farhat (Harvard University)

Maha Farhat began by summarizing the genetic basis of drug resistance, as well as presenting a construct to understand the molecular diagnostic gap. Farhat presented a prediction model using a random forest classifier to attempt to associate genotype to phenotype, accounting for potential gene-gene interaction. The model identifies the minimum set of mutations predictive of drug resistance. Farhat presented data on the predictive performance of the model, noting areas for improvement, indicating larger datasets as opportunities to further

refine and train the model.

- Video
- Presentation

A Standardized System for Grading Mutations in *Mycobacterium tuberculosis* for Association with Drug Resistance

Paolo Miotto (San Raffaele Scientific Institute)

Paolo Miotto's presentation shined light on the issue that there are no standardized measures to interpret data on TB mutation, and therefore conclude what those mutations mean in terms of detecting or predicting resistance. Miotto laid a system to standardize the grading of mutation data to predict resistance, based on extensive literature review, which covers more than 300 mutations.

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What are we trying to say here? Standardizing Next Generation Sequencing Reports for TB

Jeff Tornheim (Johns Hopkins University)

Jeff Tornheim's presentation focused on a lack of standardization and consistency of what data is recorded and reported to health systems and providers when DST tests are performed. While there are huge amounts of data that could be reported – what information do clinicians and epidemiologists want from DST test reports? How do we balance technical info with simplified data enabling quick and accurate decisions about treatment? How is that data organized and presented? These are all questions discussed by Tornheim.

- Video
- Presentation

The Genomic Epidemiology Ontology and Proof Sheet Application

Damion Dooley (University of British Columbia)

Damion Dooley presented on ontology which addresses inconsistencies between different public health databases in the vocabulary used to refer to the same kinds of data/measures. Dooley presented an open-source web-based system that helps group and associate like terms, synonyms, etc. – similar to the process by which dictionaries are created. Such efforts can provide immense value by bringing research together and clarifying trends and findings.

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Panel Discussion

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Topical Breakout Sessions

The 2017 CPTR Workshop included topical breakout sessions on a range of topics, including interactive training demonstrations on several tools developed through CPTR partnerships.

Demo and Training – Hands-on tutorial on the Interactive Tool for an Optimal Positioning of Time-to-Positivity (TTP) Results in Patients with TB

Chairs: Klaus Romero (Critical Path Institute) and Nastya Kassir (Certara)

The CPTR modeling and simulation team, in partnership with Certara, developed a quantitative model that describes the longitudinal dynamic change (based on Phase II patient-level data), which gives the ability to generate interpretable parameters that can then be related to clinically-relevant endpoints (in Phase III data). The CPTR/CERTARA team developed an interactive interface (R-Shiny application) based on the patient-level TTP data collected in 11 clinical studies, which included a total of 30 treatments (dose-ranging, monotherapy and combination therapy) administered to patients with TB. This interactive tool allows users to compare the TTP behavior over time of two chosen treatments from the total of 30 different combinations that are included in the repository. Moreover, additional TTP data can be uploaded from new trials by a sponsor to perform strategic positioning of TTP against historical TTP information. This tutorial covered the basic use of this R-Shiny application and provided hands-on examples of use, interpretation of results, and optimal positioning of new TTP results uploaded into the repository.

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Addressing Interoperability Between Data Platforms

Chair: Amanda Borens (Critical Path Institute)

Attendees participated in a group discussion of the disparate efforts to collect genotypic and phenotypic data for tuberculosis isolates as well as patient outcomes to address challenges in identifying mutations associated with drug resistance. Feedback from attendees will inform an assessment of technical challenges and opportunities associated with sharing these data between platforms and to identify opportunities to expand representation of geographic and genetic diversity in at least one repository.

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Fostering Industry and Regulatory Interactions to Advance Next Generation Sequencing for TB Diagnostics

Chair: Steven Gitterman (Food and Drug Administration)

Attendees participated in discussion and shared perspectives on what is needed to foster innovation and development in TB diagnostics, with a focus on the increased role of next generation sequencing in advancing the field. Further, participants discussed the role of regulatory oversight of databases and platforms that house sequencing data for use in research and clinical development. Input and feedback from this session will be used to outline future CPTR efforts in this space.

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Innovative Partnerships to Advance Data Sharing Across Databases

Moderator: Marco Schito (Critical Path Institute)

Session Introduction

Marco Schito (Critical Path Institute)

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Brief Updates on Database Efforts

genTB

Maha Farhat (Harvard University)

Maha Farhat presented on an interface for the analysis of genomics data – genTB. A short demo was given.

- Video

HIVE

Raja Mazumder (George Washington University)

Raja Mazumder presented on High Performance Integrated Virtual Environment (HIVE), showing a set of community tools and the importance of a biocomputer-ready pipeline.

- Video
- Presentation

GenEpiO

Damion Dooley (University of British Columbia)

Damion Dooley presented on GenEpiO and BC Centre for disease control TB data projects.

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NIAID Bioinformatics Resources

Alison Yao (National Institute of Allergy and Infectious Diseases)

Alison Yao presented on NIAID bioinformatics resources for infectious diseases. The bioinformatics resource centers were started four years ago. There are four centers, each focusing on a specific pathogen, making use of the machine learning approach.

PanACEA

Patrick Phillips (UK Medical Research Council)

Patrick Phillips presented on PanACEA and associated opportunities for data sharing. With data from completed Phase 2 and 3 studies already included in databases, the coming years mark opportunities to expand data sharing with studies currently ongoing. Phillips stressed that there is a plan to share that data

through open repository, though cautioned that there are great complexities involved in doing so.

Panel Discussion

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