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Coordination of TB diagnostics research: Enabling standards and sharing of data on the molecular basis of drug resistance

Data sharing for TB diagnostics: Needs and gaps

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Critical Path to TB Drug Regimens

Rapid TB DST Consortium

CPTR

Mission:

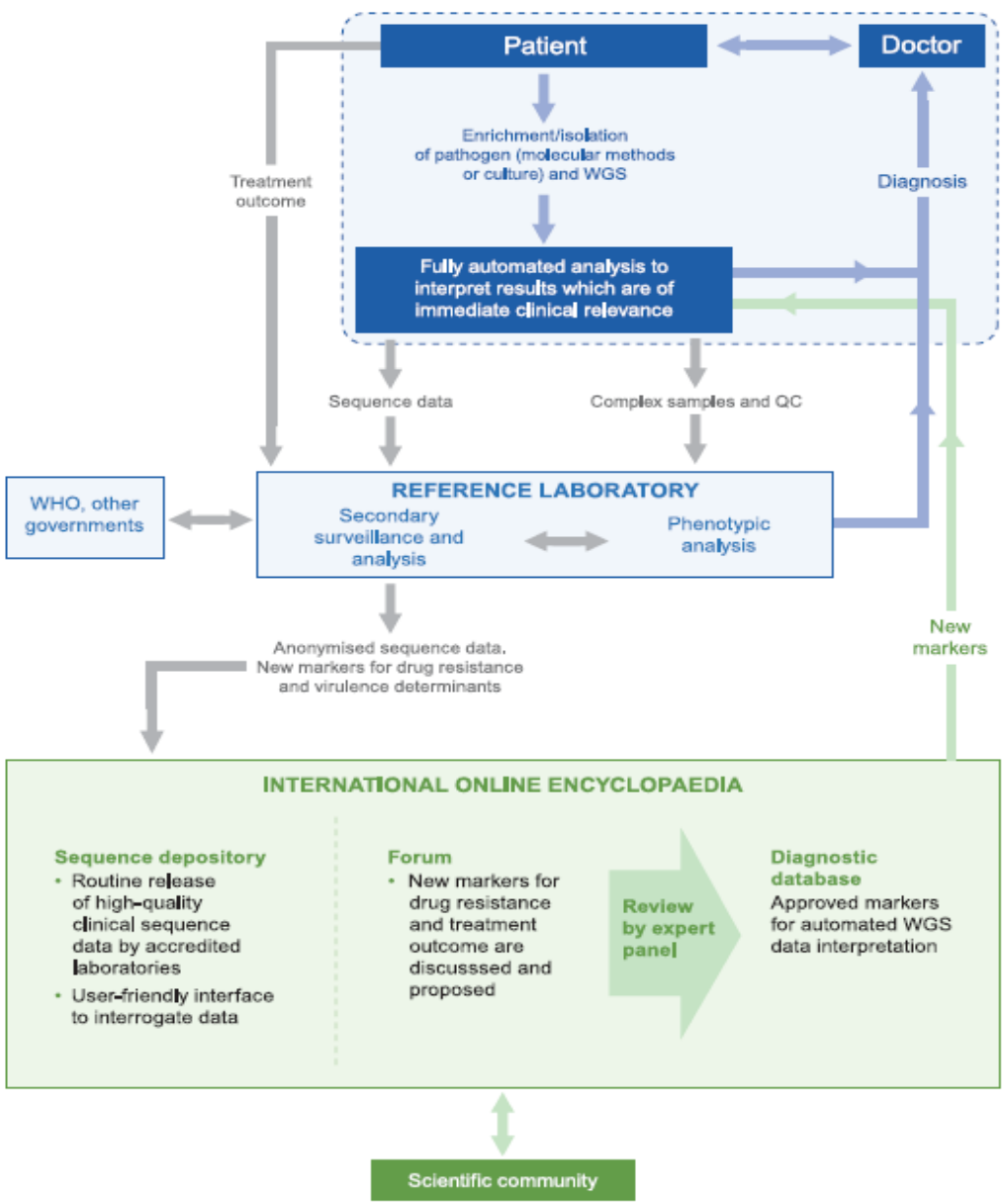
To accelerate the development of a **clinically** useful, **WHO-qualified**, regulatory approvable IVD assay for rapid TB-DST

- Such an assay is needed to support the
  - Enrolment of volunteers in clinical trials (inclusion/exclusion)
  - Commercial assay development
  - Optimize role out of new regimens (PaMZ, REMox…)
- Push for nucleic acid diagnostics to meet short TAT
- Need for a global TB drug resistance database to house genomic data for new and existing drugs
  - Who is going to use the database and why?
  - What questions do we want to address (today, 5, 10 years)?
  - Challenges for new, existing and repurposed drugs and regimens?

TB-DST Consortium stakeholders

1. Research and development
   - Level of evidence that a particular mutation correlates with resistance
   - Define sensitivity (modeling clinical impact vs. cost)
2. Ongoing global surveillance
   - Resistance data beyond HRES
   - Inform public health and clinical trials (power calc.)
   - Identify market needs and guide diagnostic algorithms
3. Biomarkers
   - Identification of a signature(s) associated with disease progression or response to therapy
4. Clinical management
   - Guide treatment decisions based on sequence information
   - Which mutations are clinically relevant?
5. Regulatory
   - Compliant with health authority requirements for IVD claims

Database structure for existing drugs



Clinical

Reference Laboratory

TB-DST Database

Koser et al. 2012. Plos Path. 8(8) e1002824

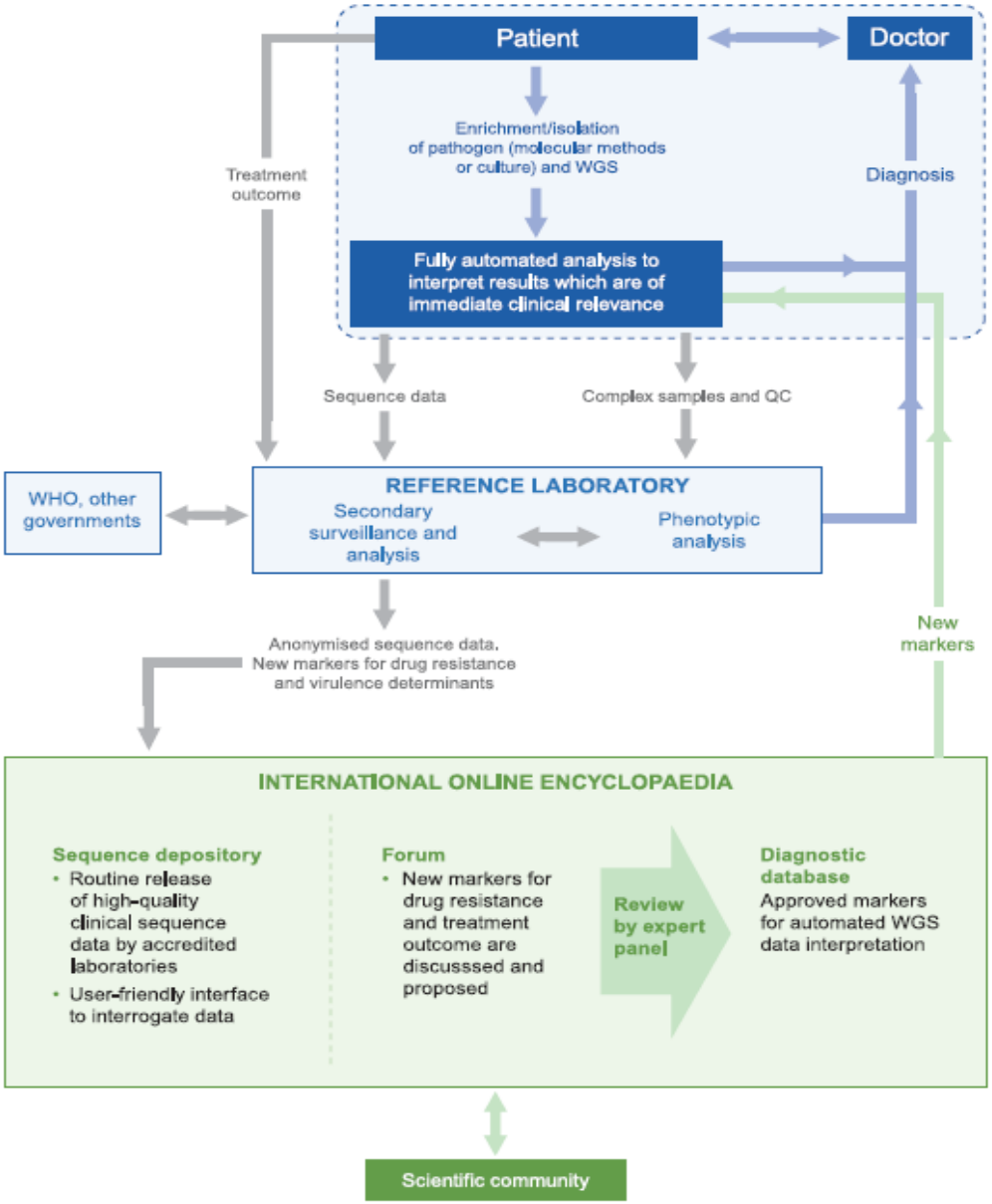
Legal issues regarding new drugs

- Pharmaceutical companies need to:
  - Include all information to authorities prior to regulatory submissions
  - Protect IP issues regarding future diagnostic applications
  - Restrict:
    a. Drug compounds for diagnostic evaluation
    b. Clinically relevant data important for developing a diagnostic DST

- CPTR effort to develop:
  - A framework whereby all stakeholders can collaborate, address concerns from drug companies and comply with regulatory policies
  - A “protected” database for a select group of participants who have scientific, technical or clinical expertise to help advance diagnostic assays for new drugs
  - Basis of the legal agreement

Proposed database for new/existing drugs

CPTR



New Drugs

- Legal agreement

Key participants
- Clinical trial groups
- Pharmaceutical Industry
- Diagnostic developers
- Scientists/clinicians
- Governments
- NGO

Clinical Trial data repository
- New TB drugs
- New regimens
- Pheno/geno
- Clinical data

Supporting preclinical data

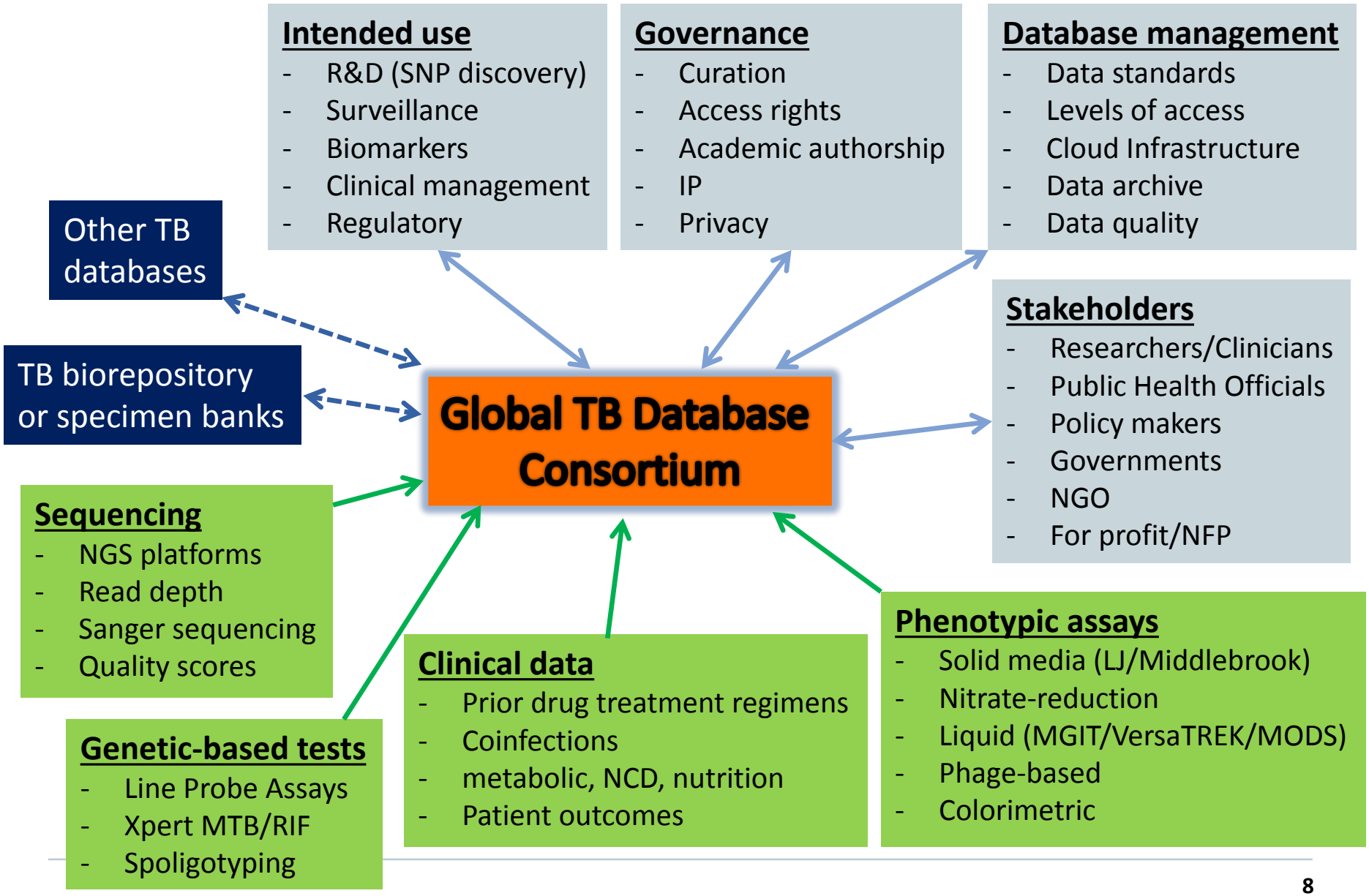
Expert Panel Review
- Policy
- Industry
- NGO
- Advocacy
- Regulators

After regulatory approval of a new drug

Gaps: Data capture and standardization

- Clinical data
  - Historically has been difficult to capture
  - Prior drug exposure(s) and clinical outcome (definitions)
  - Define standard reporting requirements (CDISC)
- Existing DST data
  - Phenotypic data (solid/liquid, direct/indirect, enzymatic)
  - Molecular data (LPA, Xpert)
  - Critical to define **data quality** (gold standard)
- Sequencing data
  - What to capture: SNPs, read depth, whole genome
  - Sequencing platforms, storage and bioinformatics?
  - Define standards for curation and base calling?
  - Define **quality of sequencing data** (quality score cutoffs)?
- Demographic data
  - Geographic location, gender, age…

Elements to consider



A few questions to address

- What do we need to capture and why?
  - Immediate needs (SNPs, MICs, and clinical data for existing drugs)
  - Next steps (read depth for heteroresistance, new drugs, and WGS)
  - Future needs (mass spec, proteomic, transcriptomics, metabolomic…)

- How to ensure quality laboratory data?
  - Conventional DST assays (ISO accreditation, EQA, annotation)
  - Sequencing platforms (common metric for determining quality scores)
  - Automated curation (alignment, SNP and indel scan, mutation matrix)
  - How to assure consistency and when is human intervention needed

  <u>Proposed key outputs:</u>

  1. Consensus quality standards for DNA sequencing
  2. Consensus for quality phenotypic data (PZA)
  3. Best practices document for downstream analysis procedures

- Utilize CPTR and NDWG infrastructure to coordinate
  - Follow up discussion, conference calls and/or face-face meeting
  - Position paper

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Sequence quality

Next generation WGS questions

- How do the different sequencing platforms compare?
- Agreement on a reference genome?
- Differences in bioinformatic software?
- How to identify mapping errors and artifacts that lead to false positive mutations?

Potential quality indicators

- Cross contamination quality checks
- Quality checks for:
  - NTB and mixed infection
  - Strand bias
  - Synonymous/non-synonymous
- Minimum coverage (>120 fold)
- Mapping quality score (>50)
- Base quality score (>30)

Additional Challenges

- Legal and policy issues
  - New Drugs: Industry collaborations
  - Existing Drugs: Country cooperation (India, China, former Soviet republics)

- How to ensure continued support?
  - Lessons learned: TB Dream, TDR, academic, surveillance, industry
  - User friendliness must be a priority
  - Bioinformatics and IT for different sequencing platforms
  - Maintenance and funding challenges (NIH, Welcome trust, MRC…)

- Link to other efforts
  - NIAID WGS contract (Broad Institute) and PATRIC database
  - Horizons 2020 (database tied to repository)