Public call for data on targeted Next-Generation Sequencing solutions for detection of drug resistance among people diagnosed with tuberculosis

Annex: Data requirements

1. Research questions
   - What is the diagnostic accuracy of targeted next-generation sequencing solutions\(^1\) for detection of drug resistance among individuals diagnosed with bacteriologically confirmed\(^2\) pulmonary TB disease, compared to phenotypic drug sensitivity testing (DST)?
   - What is the impact of targeted next-generation sequencing solutions for detection of TB drug resistance, compared to phenotypic DST, on key patient-important outcomes (see #5 for full list)?
   - What are the costs of implementing targeted next-generation sequencing solutions for detection of TB drug resistance? Are targeted next-generation sequencing solutions for detection of TB drug resistance cost-effective?
   - What are user/key stakeholder views and perspectives on the use of targeted next-generation sequencing solutions for detection of TB drug resistance?

2. Study populations
   All individuals diagnosed with bacteriologically confirmed pulmonary TB disease.
   Subpopulations:
   - Rifampicin-susceptible patients
   - Rifampicin-resistant patients
   - New TB patients
   - Previously treated TB patients
   - Patients failing a TB regimen
   - Children and adolescents <18;
   - Adults ≥18 years;
   - People living with HIV
     - CD4≥200
     - CD4<200
   - Other vulnerable groups (e.g. malnourished, DM)
   - mWRD M.TB-positive semiquantitative result (High/Moderate)
   - mWRD M.TB-positive semiquantitative result (Low/Very Low/Trace)

3. Interventions
   Targeted next-generation sequencing (tNGS) solutions for detection of drug resistance\(^1\) including the following:
   - Deeplex Myc TB
   - Deepchek Assay
   - NanoTB drug resistance assay

---

\(^1\) Solution refers to a locked design product intended for commercial use that includes DNA extraction, targeted gene amplification, sequencing of amplicons, bioinformatic analysis and a final report that provides an interpreted sequencing result classifying the result as either resistant, susceptible or uncertain

\(^2\) Confirmed positive by mWRD test, LF LAM, sputum smear microscopy, or TB culture (solid or liquid)
- Other tNGS solutions

Types of specimens:
- Sputum specimens
- Non-sputum specimens
- Culture isolates

4. Comparators
- Primary reference standard: Microbiological reference standard (MRS): phenotypic DST performed on liquid or solid culture from a respiratory specimen;
- Secondary reference standard: Composite reference standard (CRS): phenotypic DST performed on liquid or solid culture from a respiratory specimen plus whole genome sequencing

5. Outcomes

Diagnostic accuracy outcomes:
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and indeterminate rates of tNGS solutions to detect resistance to each of the following drugs:
  - Rifampicin
  - Isoniazid
  - Fluoroquinolones (Levofloxacin, Moxifloxacin)
  - Bedaquiline
  - Pyrazinamide
  - Linezolid
  - Pretomanid
  - Delamanid
  - Clofazimine
  - Amikacin
  - Ethambutol
  - Ethionamide
  - Prothionamide
  - Streptomycin

Effectiveness outcomes
- Time to results
- Time to appropriate treatment initiation (for new or previously treated patients or retreatment episode)
- Loss to follow-up
- Treatment success (cure + completion)
- Treatment failure
- Adverse events reported
- Mortality
- Emergence of incident drug resistance

Other outcomes
- Costs and cost-effectiveness
- Key user/stakeholder views and perspectives on feasibility, acceptability, and potential impact on equity of TNGS solutions