RCTs for TB diagnosis with novel molecular assays

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GenXpert MTB/Rif assay – automated RT-PCR results ready in 90 minutes
Multicentre evaluation study - excellent performance characteristics

Overall sensitivity: 92% (90-94); S+C+: 98% (97-99); S-C+: 73% (65-79)
Cape Town TB NEAT: S+C+: 96% (90-100); S-C+: 47% (37-53)
(Theron G, Peter J & Dheda K)
Overall specificity: 99% (98-100)

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

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• Diagnostic test alone has no clinical impact as an intervention
  BUT
• Diagnostic test plus treatment has measurable clinical impact

**Study Design Options**

*Observational cohort impact study*
- Open to multiple confounders
  (F-up of results poor at clinic; Pts do not return for results)

*Randomised control trial*
- Less open to confounders
  Requires narrow research question

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**Hypothesis – demonstration study**

One sputum GeneXpert MTB/RIF assay performed at the district level of care will improve TB diagnosis and the time-to-treatment for patients presenting to primary TB clinics
**FIND Xpert demonstration study design**

- **TB suspect/MDR suspect**
  - Weekly randomisation blocks
- **Target** – 10000pts
  - 5 countries

**Xpert arm**
- Sputum 1
  - Xpert (local lab/district hospital)
- Sputum 2
  - Smear MGIT (regional lab)

**Control arm**
- Sputum 1
  - Smear MGIT (local lab/district hospital)
- Sputum 2
  - Smear MGIT (regional lab)

**Speciation and MGIT DST for C+**

2 and 6 month Follow-up
  - In all TB treated and TB test positive patients

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**Study design**

**Strengths**
- Direct comparison of Xpert vs smear in programmatic setting
- Quality sub-study of smear performance
- Feasible design
- Controls for important confounders

**Weaknesses**
- Randomisation strategy
- No smear “best practice”
- Limited follow-up
- Missing important patient-outcomes e.g. Morbidity
Hypothesis – Xpert POT

One sputum GeneXpert MTB/RIF assay performed at point-of-treatment (POT) will improve TB diagnosis, time-to-treatment and TB related patient morbidity for HIV-positive and patients with TB presenting to primary level TB clinics in high HIV prevalent settings.
Study design

Strengths

- Randomisation strategy
- Xpert vs. “best practice” smear microscopy
- Internal validity of POT Xpert
- Controls for important confounders
- Patient morbidity assessment

Weaknesses

- Potential for post-randomisation bias; inability to blind
- Xpert evidence limited raising ethic issues e.g. MDR treatment initiation & treatment monitoring
- Site disparity may impact morbidity statistical power

Sputum Induction (SI)

- Safe, durable method for enhanced sputum collection
- Applicable/feasible in resource-limited settings

Tututester mobile SI unit

Battery powered-SI in Tanzania
Sputum Induction background

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Location(s)</th>
<th>n</th>
<th>HIV Prev.</th>
<th>Inclusion criteria/diagnostic algorithm</th>
<th>Smear pos no (n)(%)</th>
<th>Culture pos no (n)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell D et al.</td>
<td>Malawi</td>
<td>150</td>
<td>75/111 (79%)</td>
<td>In pt clinician referral or registering for smear neg. Empiric TB treatment</td>
<td>39/150(26) – ExpSputumObs 4/111(3.6) – i5</td>
<td>48/150(34) – ExpSputumObs 13/111(11.7) – i5</td>
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<tr>
<td>Morse M et al.</td>
<td>Gabarone, Bots</td>
<td>140</td>
<td>111/140 (79%)</td>
<td>Symptoms &amp; CXR suggestive of PTBI, no response to antibiotics</td>
<td>18/57 (32)*</td>
<td>48/57 (84)</td>
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<tr>
<td>Brown et al.</td>
<td>Middlesex, UK</td>
<td>140</td>
<td>79%</td>
<td></td>
<td>4/110 (3.6)</td>
<td>48/110 (42)</td>
</tr>
<tr>
<td>Li LM et al.</td>
<td>China (district TB clinics)</td>
<td>1648</td>
<td>648 (978)</td>
<td>Symptoms &amp; CXR suggestive of TB, previous TB Rx &amp; Sx</td>
<td>49251 (19.5)</td>
<td>94/251 (37.4)</td>
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<tr>
<td>Conde MB et al.</td>
<td>Rio de Janeiro</td>
<td>251</td>
<td>44/251 (17%)</td>
<td>Respiratory symptoms and CXR suggestive of TB</td>
<td>49251 (19.5)</td>
<td>94/251 (37.4)</td>
</tr>
<tr>
<td>Al Zahrani K et al.</td>
<td>Montreal chest insitute</td>
<td>500</td>
<td>?</td>
<td>Symptoms of PTB (unclear if clinic-radiographic or only clinical, likely both)</td>
<td>10/497 (2)</td>
<td>44/497 (9)</td>
</tr>
<tr>
<td>Parry et al.</td>
<td>Blantyre hospital Malawi</td>
<td>82</td>
<td>?</td>
<td>Clinical suspicion of active TB</td>
<td>18/82 (22)</td>
<td>30/82 (37)</td>
</tr>
</tbody>
</table>

Sputum induction RCT

- Smear negative/sputum scarce TB suspect (>18 years)
- Individual randomisation (sealed envelope)
- Target – 500

- Sputum induction arm & WHO guideline care (CXR + doctor’s review)
- Observed expectorated sputum (if possible) & WHO guideline care (CXR + doctor’s review)

- 0.5ml unprocessed stored sputa (Xpert)
- Direct FM smear, MGIT & MODS (regional lab)
- HAIN LPA on all clinical samples and for speciation/DST on Culture +

- All patients receive CXR and Doctor’s review
- 2 month follow-up for all patients on study
- Performance characteristics, Time-to-diagnosis, time to treatment, symptom score & referral to secondary hospitals; cost effectiveness
Study design

Strengths

• Feasible/practical position for ‘add-on’ test
• SI vs. “best practice” observed exp. sputum
• Controls for important confounders
• Patient relevant outcomes studied

Weaknesses

• Randomisation strategy
• Underpowered for assessing morbidity & mortality
• 2 month follow-up maybe too short for diagnostic categorisation

Conclusions

• RCT is optimal design for impact studies of molecular TB diagnostics

Important considerations for RCT study design:
1) Is there sufficient evidence to conduct an RCT?
2) What is the optimal randomisation strategy?
3) What is the currently available “best diagnostic practice” for control arm?
4) What is the follow-up strategy required to measure patient-related outcomes such as morbidity?