Xpert MTB/RIF Ultra & GeneXpert OMNI: status update

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1. **Background**
   - GeneXpert instrument
   - Xpert MTB/RIF assay

2. **Ultra**
   - FIND study
   - WHO policy
   - GLI guide

3. **Omni**
   - Features
   - Planned trials
Background
Background
GeneXpert instrument and Xpert MTB/RIF assay

Development
Validation
Policy
Limitations of the Xpert MTB/RIF cartridge

- Imperfect sensitivity for paucibacillary disease (HIV, early disease, children etc.)
- Imperfect specificity of RIF in patients with paucibacillary disease
- Imperfect sensitivity for RIF-resistance detection in case of heteroresistance
- Imperfect specificity for RIF-resistance detection due to silent mutation detection
- Imperfect specificity in NTMs (cross-reactivity)

What remains unchanged Ultra vs. Xpert MTB/RIF

- Cartridges run on the same instrument
- Simultaneous detection of MTB and RIF
- Price
Background
Limitations of the GeneXpert instrument

- Need for temperature control
- Need for constant power supply / UPS
- Dust issues
- Operated through laptop
- Not straightforward to get data out

What remains unchanged Omni vs GeneXpert
- All Cepheid cartridge will run on the Omni
- Run-times will initially be similar (to be shortened in the future)
Acknowledgements

■ Study participants

■ Study sites
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  • Department of Foreign Affairs and Trade, The Commonwealth of Australia
  • National Institutes of Health

■ Others
  • Ospedale San Raffaele
## Xpert vs Ultra

<table>
<thead>
<tr>
<th></th>
<th>Xpert</th>
<th>Ultra</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Single copy rpoB</td>
<td>Multi-copy IS6110 &amp; IS1081 + rpoB</td>
<td>Increased sensitivity: 20 CFU/ml vs 130 CFU/ml</td>
</tr>
<tr>
<td><strong>Cartridge</strong></td>
<td>25mcl tube</td>
<td>50 mcl tube</td>
<td></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Real time PCR curves</td>
<td>Melt curve analysis</td>
<td>• Improved ability to detect mutations in mixtures.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Robust detection of all mutations associated to Rifampin resistance (i.e. rpoB 533 C to G mutations).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Avoid false + for Rifampin resistance in samples with low bacterial load</td>
</tr>
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</table>
Methods

- 10 sites in 8 countries
- Reference standard: 4 cultures
- Direct comparison Xpert vs Ultra
Performance of Xpert Ultra for TB detection

Results for RIF almost identical

One Ultra-"FP"/Xpert-"TN" patient had a non-study culture+ result (from a specimen collected 1 month post-enrolment; all study cultures were negative)

\[ \Delta \text{Sensitivity} = +17\% \ (95\% \text{CI} \ +10\%, +25\%) \]

\[ \Delta \text{Specificity} = -3.2\% \ (95\% \text{CI} \ -4.7\%, -2.1\%) \]

\[ \Delta \text{Sensitivity} = +5.0\% \ (95\% \text{CI} \ +2.7\%, +7.8\%) \]
Root Cause Analysis: False-positives

- Assay issue (false calls)
  - Melt curves
  - Sequencing
- Cross-contamination
  - NC, swabs
  - Artificial sputum
  - Analysis by time/site
- Imperfect ref. standard
- Non-viable/growing MTB

False-positive cases

FIND WHO report – available on FIND website
### Specificity depending on prior TB history

<table>
<thead>
<tr>
<th>Analysis group (Culture- neg. cases)</th>
<th>Xpert Specificity (95%CI)</th>
<th>Ultra Specificity (95%CI)</th>
<th>Delta Specificity (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled (840)</td>
<td>98.0% (96.8, 98.8)</td>
<td>94.8% (93.0, 96.2)</td>
<td>-3.2% (-2.1%, -4.7%)</td>
</tr>
<tr>
<td>No History of TB (615)</td>
<td>98.4% (97.0, 99.2)</td>
<td>95.9% (94.1, 97.4)</td>
<td>-2.4% (-4.0%, -1.3%)</td>
</tr>
<tr>
<td>Any history of TB (224)</td>
<td>96.9% (93.7, 98.7)</td>
<td>91.5% (87.1, 94.8)</td>
<td>-5.4% (-9.1%, -3.1%)</td>
</tr>
</tbody>
</table>

**Figure**

Specificity depending on time since prior TB episode

Some of this may be mitigated through re-testing

Lines are running-line least squares (mean) smoothers using a bandwidth of 0.8 (Cleveland, JASA, 1979)
Results from additional studies

**Other populations showed great increases in sensitivity**
- Pediatric data
- CSF samples
- Non-HBDCs

**Modelling**
- Suggested that trade-offs will vary depending on context

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**FIND WHO report – available on FIND website**
“The current WHO recommendations for the use of Xpert MTB/RIF also apply to the use of Ultra as the initial diagnostic test for all adults and children with signs and symptoms of TB and in the testing of selected extrapulmonary specimens (CSF, lymph nodes and tissue specimens)”

“The following implementation considerations apply to Ultra:” (summarized)

- Interpretation of Ultra results same as for Xpert with the exception of ‘trace’
- Interpret ‘trace’ calls as follows:
  - HIV+, children, extrapulm. specimens: interpret ‘trace’ as true positive
  - Others: get fresh specimen and test with Ultra; use 2nd Ultra result
Algorithm 1a. Algorithm for universal patient access to rapid testing to detect MTB and rifampicin resistance incorporating Xpert MTB/RIF Ultra

Persons to be evaluated for TB¹

Collect 1 specimen and perform Ultra assay

Follow Algorithm 1 for interpretation and follow-up for:
- MTB detected other than trace¹ (any rifampicin result)
- MTB not detected
- No result, error, or invalid result

MTB detected trace

rifampicin unknown³

PLHIV⁴ and children being evaluated for pulmonary TB and persons being evaluated for EPTB

Adults being evaluated for pulmonary TB who are not at risk for HIV

Repeat Ultra assay using a fresh specimen

MTB detected other than trace

Follow Algorithm 1 for interpretation and follow-up

MTB detected trace

repeat Ultra assay using a fresh specimen

MTB not detected

• Treat with first-line regimen¹
• Repeat Ultra assay using a fresh specimen
• Conduct additional investigations to confirm or exclude resistance to rifampicin
• Review treatment based on DST result

MTB detected trace

• Treat with first-line regimen¹ unless the person has a recent history of TB treatment¹
• Conduct additional investigations to confirm or exclude resistance to rifampicin
• Review treatment based on DST result

MTB not detected

• Re-evaluate the patient clinically⁷
• Conduct additional testing in accordance with national guidelines
• Consider repeat Ultra testing
• Use clinical judgment for treatment decisions

¹ Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the diagnosis of extrapulmonary TB using CSF, lymph node, and other tissue specimen. The evaluation should include determining the person’s age, HIV-infection status, and possibility of a history of TB treatment.

² MTB detected (not trace) includes MTB detected high, moderate, low, or very low. Follow Algorithm 1 for interpretation and follow-up testing.

³ MTB detected trace results do not provide any information regarding rifampicin susceptibility or resistance.

⁴ PLHIV include persons who are HIV positive or whose HIV status is unknown, but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

⁵ Patients should be initiated on a first-line regimen according to national guidelines unless the patient is at very high risk of having MDR-TB or if a second Ultra assay indicates rifampicin resistance. Such patients should be initiated on an MDR-TB regimen.

⁶ For adults who successfully completed a course of therapy within the past 2 years (i.e., recent TB treatment), the possibility of both Ultra trace results being false-positive results because of the presence of non-viable bacilli must be considered. Clinical decisions must be made on all available information and clinical judgment; further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents, repeat Ultra testing, or culture.
Omni
TB: The need for a patient-centred approach to diagnosis

LEVEL 0: 30% seek care here
No TB diagnostics or sample referral capacity

LEVEL 1: 53% seek care here
Extremely limited TB diagnostics

LEVEL 2: 10% seek care here
Some TB diagnostics capacity

LEVEL 3: 0% seek care here
High TB diagnostics capacity, including drug sensitivity

Gene Xpert
Established in LMICs
>21'600 installed modules

Smear Microscopy
diagnosis of majority of TB cases

LPA
Culture
DST

Omni

Omni
Improvements on the Cepheid platform

- Battery operated
- Robust to dust and high temperatures
- Mobile phone interface
- Connectivity enabled
- Significantly lower cost

Expanded portfolio: Xpert, Ultra, XDR, other diseases (HIV, HCV, NG/CT, Ebola)
**General aim**

- Generate high-quality evidence on feasibility and impact of Omni on patient outcomes to drive global uptake

**Two categories of studies**

- Use of Omni for passive case finding (PCF) vs standard of care
- Use of Omni for active Case finding (ACF):
  - (i) community-based,
  - (ii) facility-based or
  - (iii) household contact screening
- Additional modelling and cost-effectiveness studies planned

**Study designs and outcomes**

- 11/13 are randomized trials
- Outcomes for PCF studies*
  - Primary: proportion rapidly diagnosed and treated
  - Key secondary: all-cause mortality at 6 months
- Outcomes for ACF studies
  - Varying by study (including feasibility, time to diagnosis/treatment, case yield etc.)

* These two outcomes and key study design features have been harmonized between studies to allow for a global analysis across all sites.
Vision for TB diagnostics in 2020

Case finding – first point of contact

1. Triage tests

Further work up & treatment – dedicated unit

2. Confirmation & rapid drug susceptibility testing (critical drugs)

Surveillance, QA, training – specialized unit

3. Comprehensive, rapid drug susceptibility testing

E-Health supported solutions
Thank you/ Questions?

FIND
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