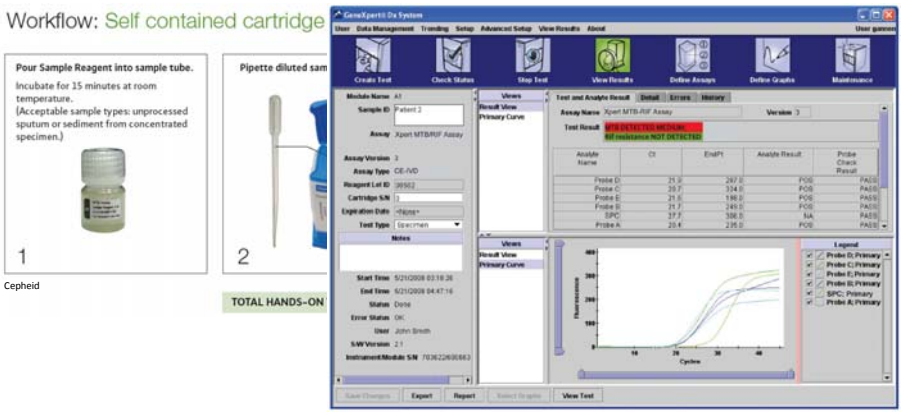
Diagnostic RCT case studies: Xpert MTB/RIF in the clinic and in the ICU

Grant Theron and Jonny Peter
on behalf of the TB-NEAT consortium
(PI: Keertan Dheda)
Lung Infection and Immunity Unit,
University of Cape Town, South Africa
grant.theron@uct.ac.za

So, what is Xpert MTB/RIF?

- An automated PCR platform that simultaneously detects TB and rifampicin resistance



In South Africa, Xpert MTB/RIF will replace smear microscopy

- WHO-approved as a frontline test for individuals suspected of TB-HIV co-infection

World Health Organization

AUTOMATED REAL-TIME NUCLEIC ACID AMPLIFICATION TECHNOLOGY FOR

'Bazookas' will help fight TB says Motsoaledi

Kerry Cullinan and Dipuo Sedibe

THE health department has bought 30 multi-million rand machines that can diagnose drug-resistant tuberculosis within two hours rather than the usual four weeks.

Health minister Aaron Motsoaledi unveiled the biggest of these GeneXpert machines, which can process 48 TB tests in a two-hour session, at Prince Mshiyeni Hospital in Durban during a World TB Day function yesterday.

South Africa is the first African

'REVOLUTION': Health Minister Aaron Motsoaledi

TB was first discovered.

Motsoaled described the machines as a "revolution", saying that these were the "bazookas" in the war against TB.

The GeneXpert machines are easy to use and 98 percent accurate. The machines have all been linked to the National Health Laboratory Service's central computers, which can monitor whether they are being used properly.

One in five South African TB patients has drug-resistant TB, thanks to years of inadequate monitoring and control of TB patients.

Motsoaled described the machines as a "revolution", saying that these were the "bazookas" in the war against TB.

However, Motsoaledi warned that technology alone could not win the war against TB. For this reason, he also launched a campaign involving house visits to homes of TB patients in areas where there is a high TB rate.

"We need to change the practice

going to visit communities with to test people for

uld also screen children for immunisations, offer HIV tests and ensure that pregnant women were attending ante-natal clinics.

"This has already started in Ethekwini which has screened 4 350 people and found 1 300 with TB susceptibility," said Motsoaledi.

By next TB Day, countrywide teams aim to visit 200 000 homes.

"This is not a once-off cam-

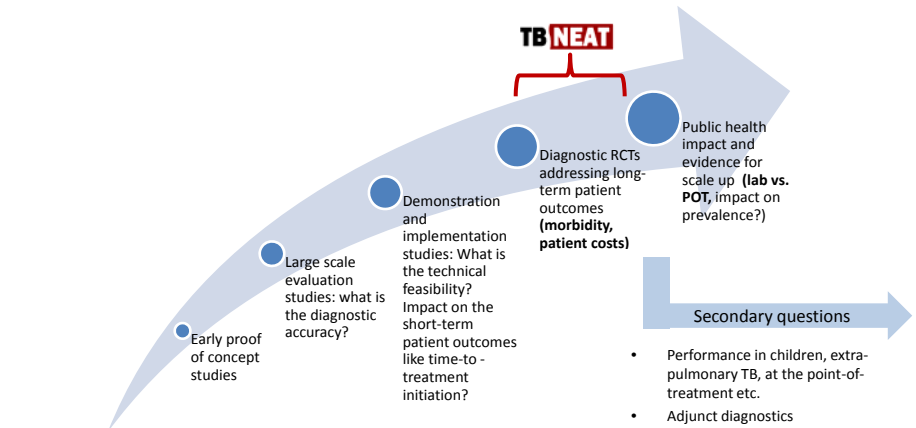
Cape Times, 25 March 2011

World Health Organization

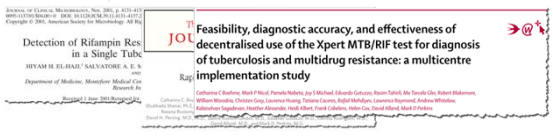
Rapid Implementation of the Xpert MTB/RIF diagnostic test

Xpert MTB/RIF research gaps

Beyond diagnostic accuracy to patient outcomes



- Performance in children, extra-pulmonary TB, at the point-of-treatment etc.
- Adjunct diagnostics
- Identification of the most infectious patients
- **Performance in different settings, e.g. in the intensive care unit or at the clinic**


Detection of Rifampin Res in a Single Tube

HIYAM H. EL-HAJJ,† SALVATORE A. E. S

Department of Medicine, Montefiore Medical Cen Research Fe

Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study

A RCT of a point-of-treatment Xpert MTB/RIF for the diagnosis of TB at primary care clinics in HIV prevalent, resource-limited settings.

- We don't know the impact of Xpert on patient health, or if it feasible to do the assay the clinic
- **Hypothesis:** One sputum Xpert MTB/RIF performed at the point-of-treatment will improve TB-related morbidity and patient-level costs in individuals suspected of TB who present to primary level clinics in high burden, HIV-prevalent settings.
- **Setting and patient numbers:**
  1. 5 study sites in 4 countries (Cape Town, Durban, Harare, Lusaka, Mbeya)
  2. Enrolment target of approximately 1600 patients (March 2011 – February 2012)
  3. Patients are recruited from (peri)-urban primary care clinics. An Xpert assay is performed on site by a study nurse.

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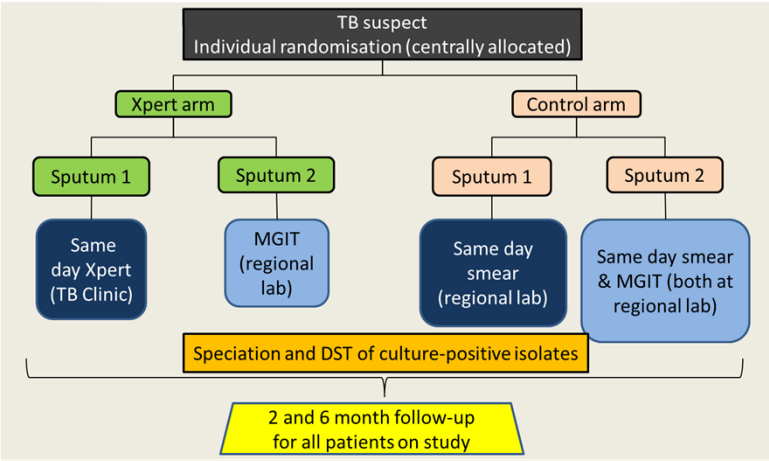
Xpert RCT: Patient flow



Each patient also receives: (i) TB-related morbidity score (at 0, 2 and 6 months), (ii) a health and cost questionnaire (0, 2 and 6 months), (iii) a CXR at 0 months and at follow-up if symptomatic

→ Patients who are TB positive are referred to the DOTS programme at the clinic

Xpert RCT: Challenges

- Accurate diagnostic impact studies require randomisation
- But few diagnostic RCTs exist, especially for TB!
- Outline of challenges in the design of the study:
  1. Selecting outcomes that add to earlier work
  2. What do we compare Xpert too?
  3. How many patients do we need to recruit?
  4. How should patients be randomised?
  5. Setting-specific limitations
  6. How to keep the study ethically- and scientifically-sound in a rapidly changing environment?

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1. Xpert RCT: Primary outcomes

- At study start, improved accuracy established but improved time-to-treatment initiation was not known
- Primary outcomes for our study:
  1. Time-specific (2 and 6 month) TB-related morbidity score between arms
  2. Technical feasibility a clinic point-of-treatment Xpert
  3. Impact on patient-level costs and quality-of-life compared between arms
  4. How does the culture-positive default rate compare across arms?
  5. Time-to-treatment initiation

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Xpert RCT: Where in the evidence pipeline does this study lie?

It uniquely aims to measure:

1. Long-term patient-related outcomes (such as impact on morbidity)
2. Patient-level costs and impact on quality of life
3. Test feasibility at the clinic

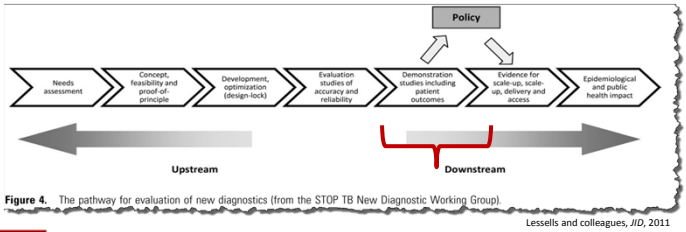

Figure 4. The pathway for evaluation of new diagnostics (from the STOP TB New Diagnostic Working Group).

Lessells and colleagues, *JID*, 2011

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2. Xpert RCT: Setting-specific considerations

Striking a balance between scientific rigour, practical constraints, and keeping things programmatically relevant:

1. Practicality of placing Xpert at the clinic (keeping it nurse-operated is not possible at all sites)
2. How do we measure the feasibility and user experience of test at the clinic?
3. How do we ensure we do not bias the study against smear-microscopy? What about same-day smear?
4. How to we ensure patients are fairly compensated but do not unfairly bias them to wait for their same-day result?

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3. Xpert RCT: Choosing the comparison test

How do we choose what to compare Xpert too?

- Difficult issue: not many TB Dx RCTs → In our study patients receive either Xpert+culture or smear+culture
- Previous RCTs of Xpert have included a more rigorous gold standard (multiple solid and liquid cultures)
- Important to perform tests in the comparison group that most are likely to be used in programmatic settings (Dx accuracy not our primary outcome)
- A criticism is our inclusion of culture in each arm → ethically difficult
- Therapeutic strategies need to be standardised across arms and sites → we are trying to detect benefits associated with the earlier diagnosis of disease (a package comprised of diagnosis & treatment)

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4. Xpert RCT: Sample size calculations

Using a standardised TB morbidity score as the primary outcome:

	Expected baseline value of TB score	Expected value of TB score at 2 months
	Mean (SD)	Mean (SD)
Xpert arm	6.5 (2.0)	2.5 (2.0)
Smear arm	6.5 (2.0)	3.0 (2.0)

- To detect the smallest clinically NB difference in score at 2 months (0.5), we need 250 TB cases in each arm (80% power)
- At a prevalence of ~30% this equals ~1600 patients
- But the prevalence has been lower than anticipated…

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5. Xpert RCT: Randomisation

- This study has morbidity-related endpoints
- Critical that Xpert is not reserved for those perceived to benefit the most from it (e.g. patients who appear the most sick)
  - Per patient vs. weekly block randomisation
  - Central randomisation vs. on-site (e.g. via sealed envelopes)
- Central randomisation by the data manager proved to be the most suitable option
- But other options exist → SMS-based systems

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6. Xpert RCT: Ethical considerations

- Xpert is more accurate than smear – can we justify giving half our patients an inferior test?
  - Culture in both arms
  - Hardly any data on if 2-3 weeks difference in treatment initiation in a clinic makes a difference
  - Xpert is not the standard-of-care yet in most countries
  - The same day smear-result and CXRs are benefits patients do not receive upfront in routine care
- Is it ethical for nurses to perform the test?
  - Formal training and passing of test
  - Monthly examination and inspection

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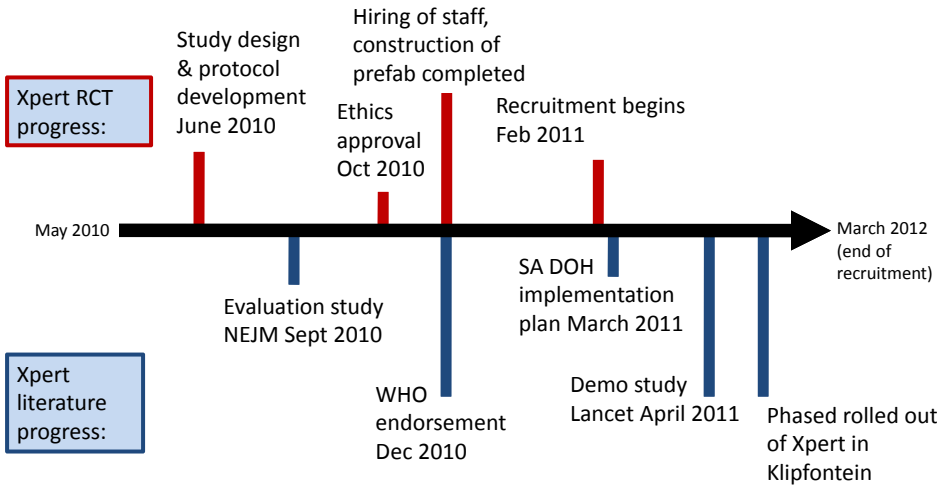
Xpert RCT: Ethical and other challenges in a rapidly moving field



→ Approx. 4 new Xpert publications per month!

A quick word about another RCT: the impact of Xpert in the ICU

- **Hypothesis:** One Xpert MTB/RIF assay performed on the tracheal aspirate of mechanically ventilated patients clinically suspected of pulmonary TB in the intensive care unit will reduce the duration of mechanical ventilation and length-of-stay
- Patients randomised to Xpert+culture or smear+culture
- Here culture is in poor gold standard (high rates of contamination by non-AFB)
- Primary outcomes:
  - Duration of mechanical ventilation
  - Length of ICU stay

Conclusions

- Balancing scientific rigor with practical constraints in difficult (especially in multicenter studies)
- Maintaining relevance in a rapidly changing landscape can be hard
- Patient outcomes are not just dependent on diagnosis → important to keep in mind that a diagnostic + treatment package is often evaluated
- Measuring long-term patient outcomes (e.g. morbidity) can require large patient numbers

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