Performance evaluation of the Xpert MTB/XDR assay

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Disclosures

- Funding for this study was received from the Foundation of New Innovative Diagnostics (FIND)/KFW
- Cepheid provided the Xpert MTB/XDR cartridges for the study

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Drug-resistant TB

- In 2019, ~500 000 individuals developed Rif-R TB, of which 78% developed MDR-TB
- The **rapid diagnosis** and appropriate treatment of **drug-resistant TB** (DR-TB) is therefore essential to **prevent significant morbidity**, **mortality** and **further transmission** of TB disease
- **Available second-line** diagnostics require **laboratory infrastructure** – pDST and Bruker-Hain MTBDR*s*l/ LPA
- **Xpert MTB/XD**R assay is a **lower complexity**, **automated** molecular assay for broader resistance detection suitable for use at lower levels in the healthcare system

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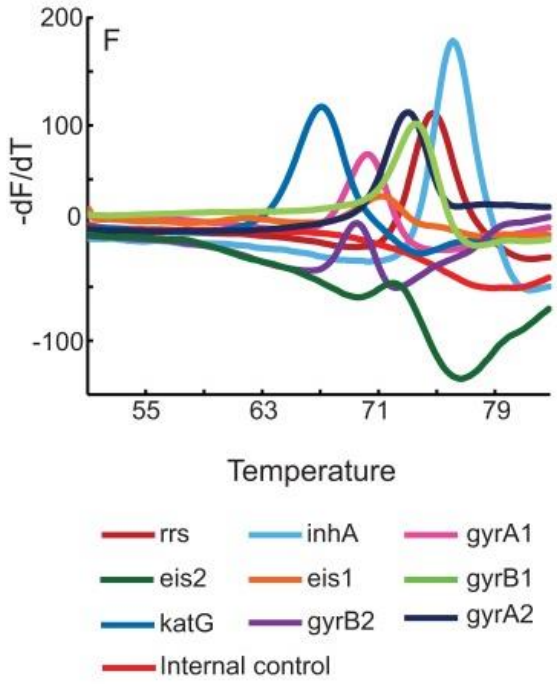
Xpert MTB/XDR Assay

- Results in <90 minutes
- Same easy-to-use process as Xpert MTB/RIF Ultra
- Performed on existing GeneXpert® platform equipped with 10-color modules
- On board internal controls: Sample Volume Adequacy (SVA), Probe Check Control (PCC), Sample Processing Control (SPC)
- Detects resistance to:
  - INH- katG, inhA pt, ahpC, fabG1
  - ETH – inhA promoter
  - FQs- gyrA, gyrB
  - SLID (AMK, KAN, CAP) - rrs, eis

10-color modules can also run any other Xpert test



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Study Synopsis

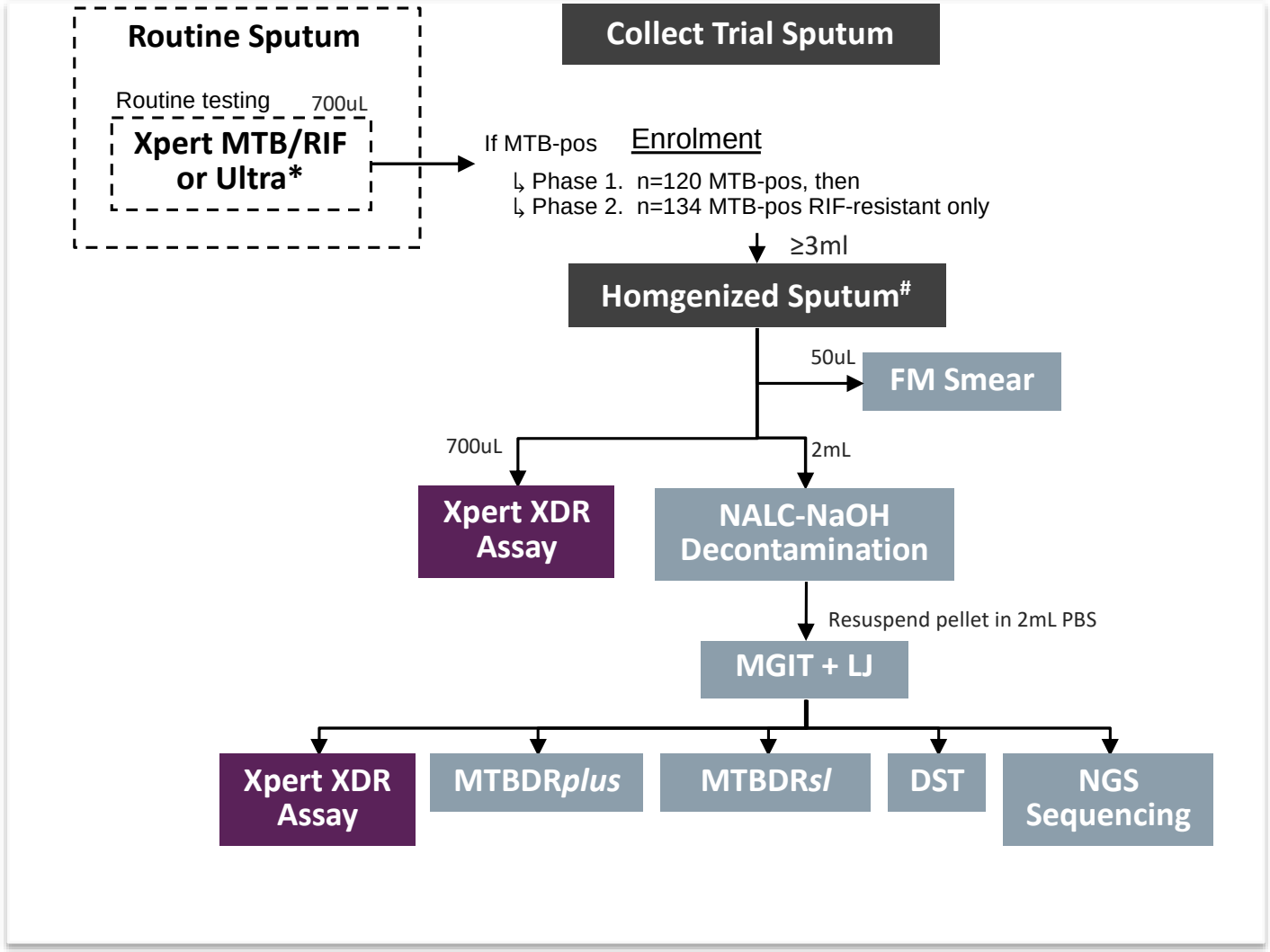
Clinical sites with high rates of drug-resistant TB

- Phase II: Multicentre Clinical Study to Assess the Performance of the Xpert MTB/XDR Assay for INH- and Second-line Resistance Detection
- Sites
  - Mumbai, India: P.D. Hinduja Hospital
  - Delhi, India: National Institute of Tuberculosis and Respiratory Diseases
  - Chisinau, Moldova: Phthisiopneumology Institute "Chiril Draganiuc”
  - South Africa: University of the Witwatersrand, Johannesburg
- Primary Objectives: **clinical diagnostic accuracy** and **operational characteristics** of the Xpert MTB/XDR assay
- Secondary objectives: Assess additional **Xpert MTB/XDR performance characteristics**, including **direct performance versus performance on cultured samples**, **performance between sites**, by **smear status**, by **gene target and compared to Hain MTBDRplus and MTBDRsl**

Trial Design

Inclusion Criteria

- ≥ 18 years
- Symptoms suggesting pulmonary TB, i.e. persistent cough, **and** at least one DR-TB risk factor
- MTBC-positive and valid RIF-resistance profile by Xpert MTB/RIF Ultra
- Provision of informed consent
- Production of an adequate quantity (≥4mL) of sputum



≥ 3ml of sputum is required for the trial. This can be achieved through an individual sputum or pooling of serially collected sputa, homogenized with glass beads.

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Participant cohort

- 710 participants were approached and enrolled at the four sites (Jul 2019 – Mar 2020)
- All participants were diagnosed with TB (as reported by the Xpert G4 or Xpert MTB/RIF Ultra assay) and all had a valid RIF result
- 611/710 had a MTBC-positive MGIT and were included in the analysis
- Reference standard = DST and/or WGS

N	**611**
Demographics or clinical characteristics	
Median age [min - max] (years)	37 [18, 77]
% Female sex [n/N]	35% [214/611]
% HIV positive [n/N]	16% [69/425]
% Xpert G4 or Ultra RIF-R [n/N]	81% [494/611]
% smear negative [n/N]	24% [146/609]

Indeterminates

	%	n/N
MTB invalid	2.96	21/709
Indeterminate (drug resistance)		
INH resistance	0.30	2/657
ETH resistance	0.15	1/657
FLQ resistance	1.37	9/657
AMK resistance	3.50	23/657
KAN resistance	3.20	21/657
CAP resistance	2.89	19/657

Xpert MTB/XDR invalid rate higher for smear negative samples than for smear positive samples (6.2% compared with 0.2%)

Xpert MTB/XDR compared to composite reference standard

	Direct		Culture isolate	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
MTB Detection	98.4 (96.9-99.2)		100 (94.2-100)	
INH resistance	94.3 (91.7-96.1)	100 (94.1-100)	94.6 (92.1-96.3)	100 (94.2-100)
ETH resistance	54.3 (48.7-59.7)	99.5 (97.0-100)	56.3 (50.8-61.7)	98.2 (95.0-99.4)
FLQ resistance	94.5 (90.5-96.9)	99.3 (97.3-100)	95.0 (91.2-97.3)	100 (98.4-100)
AMK resistance	73.2 (62.1-82.1)	99.5 (98.1-99.9)	73.6 (62.8-82.2)	99.8 (98.6-100)
KAN resistance	86.2 (80.6-90.4)	98.4 (96.0-99.4)	87.7 (82.4-91.6)	99.1 (97.0-99.8)
CAP resistance	60.9 (49.8-71.0)	99.8 (98.5-100)	59.8 (49.0-69.7)	100 (98.9-100)

The *composite reference standard* was defined as "resistant" if either WGS or pDST was resistant, and defined as "susceptible" if both pDST and WGS were susceptible

LPA and Xpert MTB/XDR compared to culture DST

	LPA (Indirect)		XDR (Direct)	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
INH resistance	93.0 (90.0-95.0)	100 (94.0-100)	94.0 (92.0-96.0)	100 (94.0-100)
FLQ resistance	95.0 (91.0-97.0)	99.0 (97.0-100)	95.0 (91.0- 97.0)	99.0 (97.0-100)
AMK resistance	73.0 (62.0-82.0)	100 (98.0-100)	73.0 (62.0-82.0)	100 (98.0-100)
KAN resistance	86.0 (81.0-90.0)	98.0 (96.0 -99.0)	86.0 (81.0-90.0)	98.0 (96.0 -99.0)
CAP resistance	61.0 (50.0-71.0)	100 (99.0-100)	61.0 (50.0-71.0)	100 (99.0-100)

The *composite reference standard* was defined as "resistant" if either WGS or pDST was resistant, and defined as "susceptible" if both pDST and WGS were susceptible

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Xpert MTB/XDR (Direct) compared to composite reference standard stratified by smear status

	Smear positive	Smear negative	Specificity (%, 95% CI)
	Sensitivity (%, 95% CI)	Sensitivity (%, 95% CI)	
INH resistance	94.3 (91.3-96.3)	94.1 (87.1-97.6)	100 (94.1-100)
ETH resistance	54.8 (48.5-60.9)	50.8 (38.2-63.3)	99.5 (97.0-100)
FLQ resistance	96.1 (91.7-98.3)	89.1 (77.1-95.5)	99.3 (97.3-99.9)
AMK resistance	76.1 (63.9-85.3)	53.8 (26.1-79.6)	99.5 (98.1-99.9)
KAN resistance	87.4 (81.4-91.8)	78.8 (60.6-90.4)	98.4 (96.0-99.4)
CAP resistance	60.8 (48.7-71.7)	54.5 (24.6-81.9)	99.8 (98.5-100)

The *composite reference standard* was defined as "resistant" if either WGS or pDST was resistant, and defined as "susceptible" if both pDST and WGS were susceptible

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Conclusions

- Similar performance demonstrated using Xpert MTB/XDR assay on direct sputum and MGIT
- Sensitivity >90% for INH and FLQ
- Specificity >98% for all drug targets
- Almost identical performance between LPAs and Xpert MTB/XDR assay
- Xpert MTB/XDR assay demonstrated better performance on smear positive specimens

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