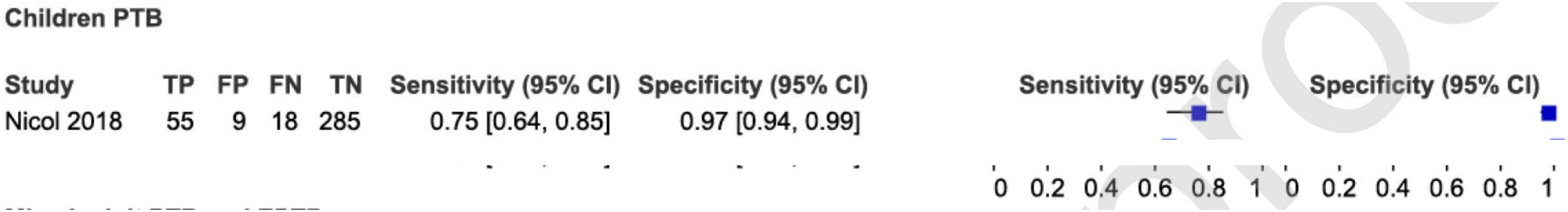
Xpert Ultra

Xpert ultra in Children

Authors and year	Population	Samples	Sensitivity	Specificity
Nicole 2018	367 Children <15 yrs, median age 3 IQR 1.25-6 yrs 8.5% previously treated for TB HIV + 19%	Banked IS, 76 microbiologically confirmed (composite reference standard positive xpert, ultra or culture)	Xpert 63% (48/76, 95%CI 51–74) Ultra 74% (56/76, 95%CI, 62–83), an incremental benefit of 11% Culture 83%	Ultra was 97% (225/233, 95%CI 93–99) In previously treated:96%, 23/34, 95%CI 79–100) Treatment-naïve 97%, 249/256, 95%CI 94–99)



Pediatr Infect Dis J. (2018) 37:e261–3.

Xpert ultra in induced sputum/NP aspirates

- 195 children [median age 23·3 months, 32(16·4%) HIV-infected]
- One induced sputum and nasopharyngeal aspirate
- Results: 130 had two nasopharyngeal aspirates
- Culture confirmed: 40(20·5%)
- Ultra positive on nasopharyngeal aspirates: 26(13·3%) and Induced sputum in 31(15·9%)

Zar et al. AJRCCM Articles in Press. Published on 05-August-2019 as 10.1164/rccm.201904-0772OC

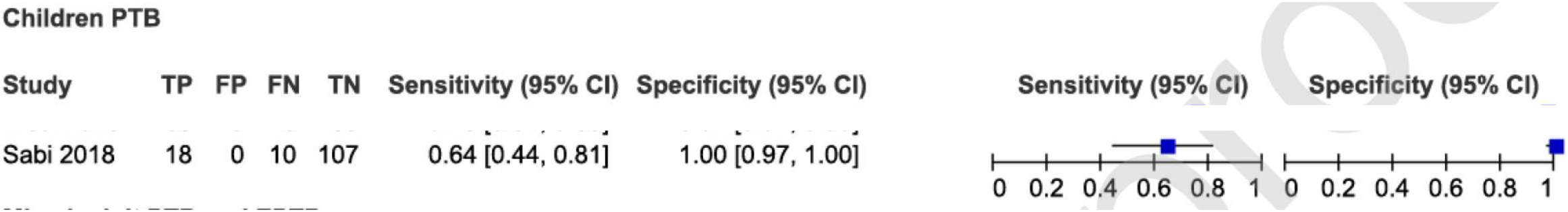
Xpert ultra in induced sputum/NP aspirates

- Sensitivity and specificity of Ultra on one nasopharyngeal-aspirate: 46% and 98% respectively
- **Similar by HIV status**
- Sensitivity and specificity of Ultra on one induced sputum were 74·3% and 96·9% respectively.
- Sensitivity of Ultra
  - two nasopharyngeal aspirates was 54.2%
  - combining one nasopharyngeal aspirate and one induced sputum: 80%.
  - two induced sputum: 87.5%

Zar et al. AJRCCM Articles in Press. Published on 05-August-2019 as 10.1164/rccm.201904-0772OC

Xpert ultra in Children

Authors and year	Population	Samples	Sensitivity	Specificity
Sabi et al 2018	215 children across two sites in Tanzania, Median age: 5.4 years (IQR 1.5 to 9.9 years), HIV + 52%.	Frozen sputum samples Culture confirmed: 28(13%)	Ultra 64% (18/28, 95%CI 44–81) Xpert 54% (15/28, 95%CI 34–73) 11% sensitivity increase	Ultra 100 (95% CI 97-100)



J Infect. (2018) 77:321–7.

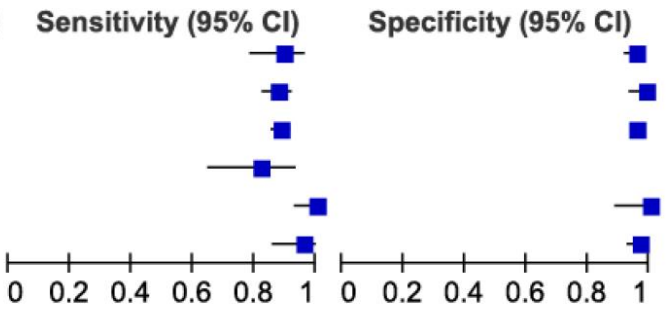
Xpert ultra in children

- Good potential
- Limited experience in children: Three studies on stored samples
- Samples used were stored Induced sputum in two and NP aspirate/Induced sputum in one
- Sensitivity: 64-75% (75% (95% CI 64–85%); 64% (95% CI 44–81%); 74%
- Proportion of HIV infection 19- 50%
- Specificity: 96-100% [96%, 97% (95% CI 94–99%) and 100% (95% CI 97–100%)]
- Need for more studies on GA/IS/Stool/EPTB

Quantitative synthesis of all the studies

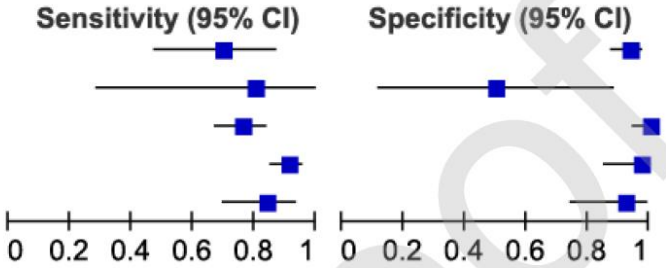
Adult PTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	50	8	6	173	0.89 [0.78, 0.96]	0.96 [0.91, 0.98]
Chakravorty 2017	175	1	25	76	0.88 [0.82, 0.92]	0.99 [0.93, 1.00]
Dorman 2018	408	43	54	934	0.88 [0.85, 0.91]	0.96 [0.94, 0.97]
Hodille 2019	27	0	6	0	0.82 [0.65, 0.93]	Not estimable
Kolia-Diafouka 2019	48	0	0	30	1.00 [0.93, 1.00]	1.00 [0.88, 1.00]
Opota 2019	45	5	2	144	0.96 [0.85, 0.99]	0.97 [0.92, 0.99]



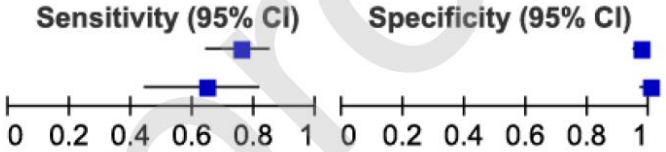
Adult EPTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bahr 2018	16	7	7	100	0.70 [0.47, 0.87]	0.93 [0.87, 0.97]
Chin 2019	4	3	1	3	0.80 [0.28, 0.99]	0.50 [0.12, 0.88]
Perez-Risco2018	82	0	26	60	0.76 [0.67, 0.84]	1.00 [0.94, 1.00]
Sun 2019	120	1	12	33	0.91 [0.85, 0.95]	0.97 [0.85, 1.00]
Wu2019	36	2	7	23	0.84 [0.69, 0.93]	0.92 [0.74, 0.99]



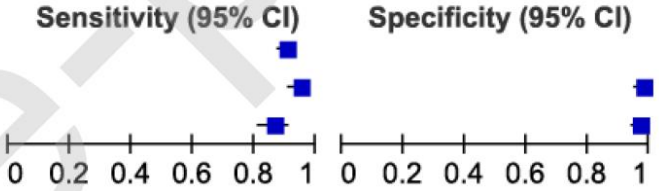
Children PTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	55	9	18	285	0.75 [0.64, 0.85]	0.97 [0.94, 0.99]
Sabi 2018	18	0	10	107	0.64 [0.44, 0.81]	1.00 [0.97, 1.00]



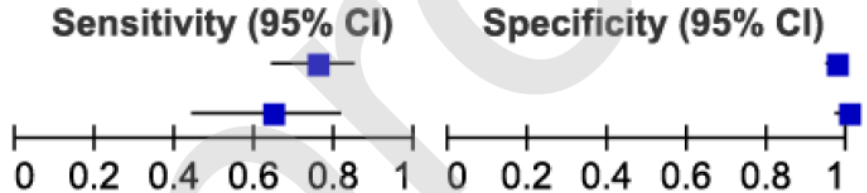
Mixed adult PTB and EPTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bisognin 2018	345	0	37	0	0.90 [0.87, 0.93]	Not estimable
Piersimoni 2019	165	4	9	181	0.95 [0.90, 0.98]	0.98 [0.95, 0.99]
Wang 2019	169	8	27	238	0.86 [0.81, 0.91]	0.97 [0.94, 0.99]



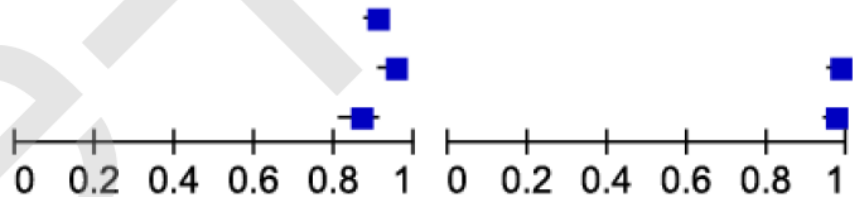
Children PTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	55	9	18	285	0.75 [0.64, 0.85]	0.97 [0.94, 0.99]
Sabi 2018	18	0	10	107	0.64 [0.44, 0.81]	1.00 [0.97, 1.00]



Mixed adult PTB and EPTB

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bisognin 2018	345	0	37	0	0.90 [0.87, 0.93]	Not estimable
Piersimoni 2019	165	4	9	181	0.95 [0.90, 0.98]	0.98 [0.95, 0.99]
Wang 2019	169	8	27	238	0.86 [0.81, 0.91]	0.97 [0.94, 0.99]



Sub group analysis..

- **Detection of pulmonary TB**
  - summary sensitivity and specificity were 88.5% (95% CI 82.1–92.9%) and 96.7% (95% CI 95.1–97.8%), respectively
- **Detection of extrapulmonary TB**
  - Pooled sensitivity 85.1% (95% CI 76.7–90.8%) and pooled specificity 95.7% (95% CI 87.9–98.6%)
- **Detection of TB in children**
  - only two studies available and the samples used both were sputum
  - Sensitivity 75% (95% CI 64–85%) in one study with a proportion of 19.4% HIV coinfected and 64% (95% CI 44–81%) in another with a 50% HIV infection
  - Specificity high in both studies, being 97% (95% CI 94–99%) and 100% (95% CI 97–100%).

Sub group analysis..

- **Detection of TB in high or low prevalence settings**
  - High TB prevalence: 10 studies
    - Pooled sensitivity: 84.9% (95% CI 79.9–88.8%)
    - Pooled specificity: 96.2% (95% CI 95.0–97.1%)
  - Low TB prevalence: 6 studies
    - Pooled sensitivity: 92.0% (95% CI: 83.7–96.3%)
    - Pooled specificity: 98.3% (95% CI: 95.2–99.4%)
- **Performance of Xpert Ultra in RIF resistance detection**
  - Only 4 studies reported data on RIF resistance detection
  - summary sensitivity: 95.1% (95% CI: 91.6–97.2%)
  - summary specificity: 98.9% (95% CI: 97.6–99.5%)

Comparative analysis

- **TB detection**
  - 14 studies with comparative data for TB detection
  - **Xpert Ultra** yielded a **higher sensitivity at 88.1%** (83.1%–91.8%), compared to Xpert MTB/RIF sensitivity of 72.5% (64.6%–79.1%), and a **lower specificity at 96.2%** (94.8%–97.3%) compared to Xpert MTB/RIF specificity of 98.9% (97.9%–99.4%).
  - PTB: 9 studies
    - diagnostic sensitivity of Xpert Ultra reached **89.2%** (82.1%–93.7%) compared to 77.6% (65.0%–85.2%) of Xpert and the specificity was 96.7% (95.1% to 97.8%) compared to Xpert MTB/RIF of 99.1% (97.7% to 99.7%)
  - EPTB: 6 studies
    - diagnostic sensitivity and specificity of the Xpert Ultra for EPTB were **85.6%** (76.7%–91.5%) and 94.7% (87.0%–97.9%), whereas the Xpert for EPTB were 64.1% (50.0%–76.1%) and 98.5% (95.6% to 99.5%), respectively
- **RIF resistance detection**
  - pooled sensitivity of Xpert was 95.1% (95% CI: 91.6–97.2%), which was similar to the Xpert Ultra (95.1%) and pooled specificity of Xpert was 98.5% (95% CI: 97.2–99.2%), which was lower than the Ultra (98.9%)

- Thanks

Urinary LAM in PTB and LN TB

UrineLAM in

- For detection of lipoarabinomannan antigen of mycobacteria in urine, lateral flow assay for Lipoarabinomannan, (Determine TB LAM Ag, from AlereTM) was used
- Fresh urine samples used within 8 hours if kept at room temperature

Presumed intra thoracic TB

- N: 280; mean age 8.6 years ± 3.90
- ZN smear positive: eight (2.8%)
- MGIT positive: 50 (17.8%)
- GeneXpert positive: 56 (20%)
- LAM assay in confirmed TB sensitivity of 73.2%, specificity 73.2%, PPV 48.1% and NPV 88.9%.

LAM in LNTB

- N=101 mean age 10.27 years ± 3.36
- ZN smear positive: 3 (2.9%)
- GeneXpert positive: 23 (22.7%)
- MGIT positive: 9 (8.9%)
- LAM: sensitivity was 76%, specificity 69.7%, PPV 45.2% and NPV 89.8%

LAM in Probable TB

- Probable TB (microbiologically confirmed and unconfirmed TB): specificity improved to 93% and PPV to 90.7%
- Probable LN TB: specificity 91.3% and PPV to 88%

LAM in Pediatric TB

- N 61 (suspected TB) (age 0-14 years)
- Probable TB 49 (21 confirmed and 28 unconfirmed)
- The urinary LAM level was higher in subjects with TB (1.80+1.02) mg/l compared to non-TB group (0.46+0.3) mg/l; $p<0.001$(independent t-test)
- If cut off 0.98 mg/L: Urine LAM had 83% sensitivity and 85% specificity
- If cut off 1.69: 33% sensitivity and 60% specificity

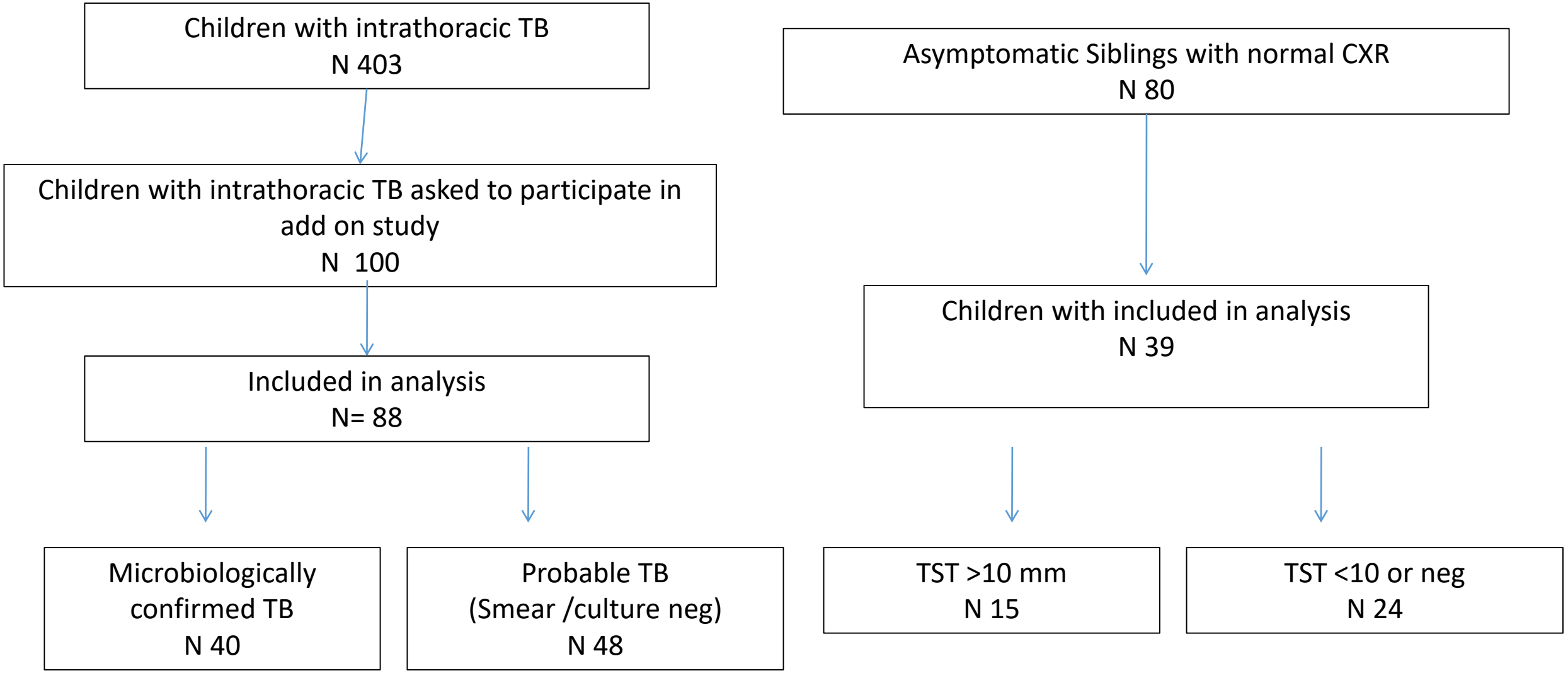
Journal of Clinical and Diagnostic Research. 2017 Mar, Vol-11(3): EC32-EC35

Urinary LAM

- Easy to perform, Good potential in pediatric TB
- Need to improve techniques to improve sensitivity and specificity

Biomarkers in TB Diagnosis and Predicting outcome

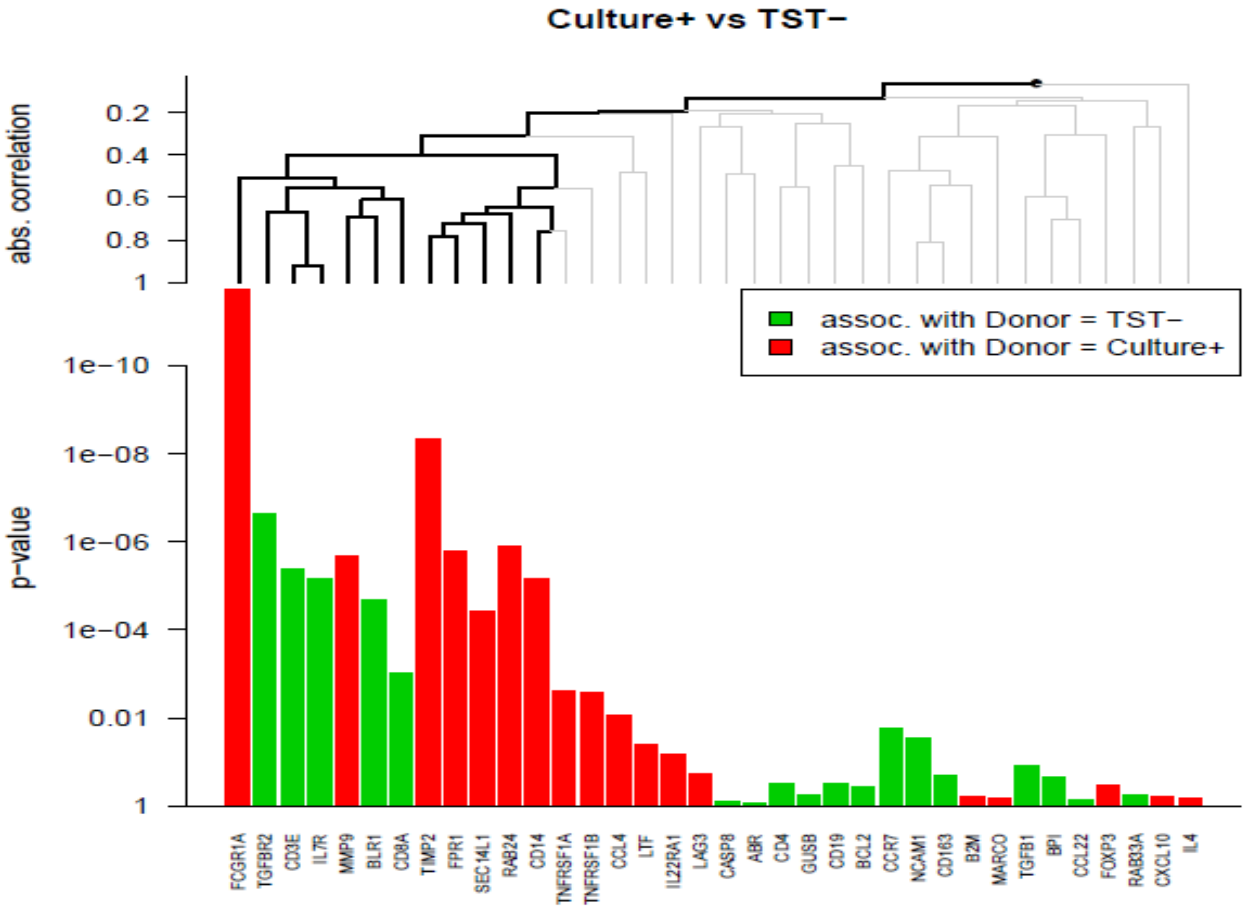
- **Point of care test for diagnosis**: Tested microbiologically confirmed intrathoracic TB, Probable Tb and sibs (Tb infection and no infection)
- Prediction of outcome
- Prediction of development of TB


Children with intrathoracic TB
N 403
Children with intrathoracic TB asked to participate in add on study
N 100
Included in analysis
N= 88
Microbiologically confirmed TB
N 40
Probable TB
(Smear /culture neg)
N 48
Asymptomatic Siblings with normal CXR
N 80
Children with included in analysis
N 39
TST >10 mm
N 15
TST <10 or neg
N 24

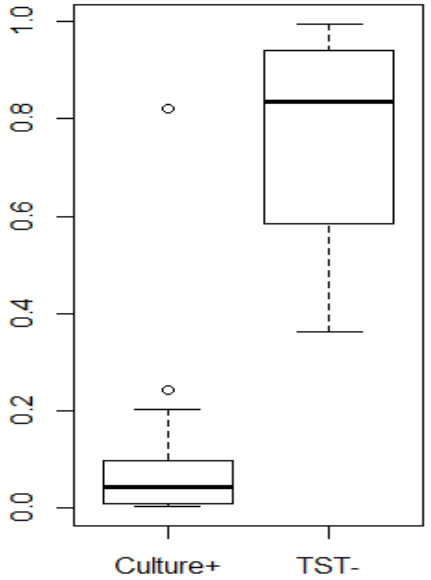
Biomarker: point of care diagnostic test

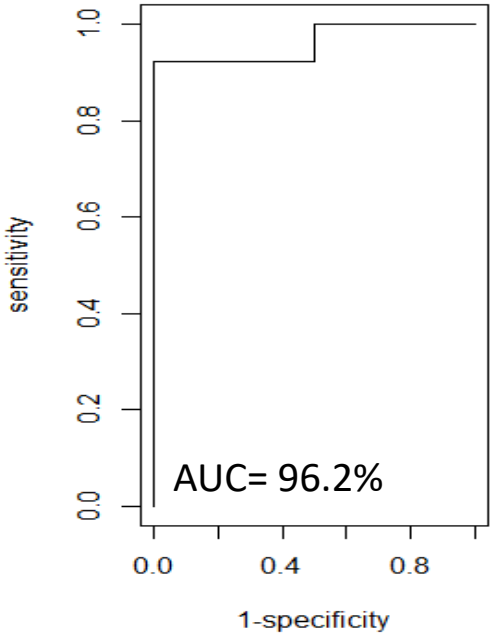
- "upstream" towards culture-positive TB on the TB disease spectrum (CD14, FCGR1A, FPR1, MMP9, RAB24, SEC14L1, and TIMP2)
- "downstream" towards a decreased likelihood of TB disease (BLR1, CD3E, CD8A, IL7R, and TGFBR2),
- A biomarker signature consisting of BPI, CD3E, CD14, FPR1, IL4, TGFBR2, TIMP2 and TNFRSF1B separated children with TB from asymptomatic siblings (AUC of 88%).

Sci Rep. 2016 Jan 4;6:1852

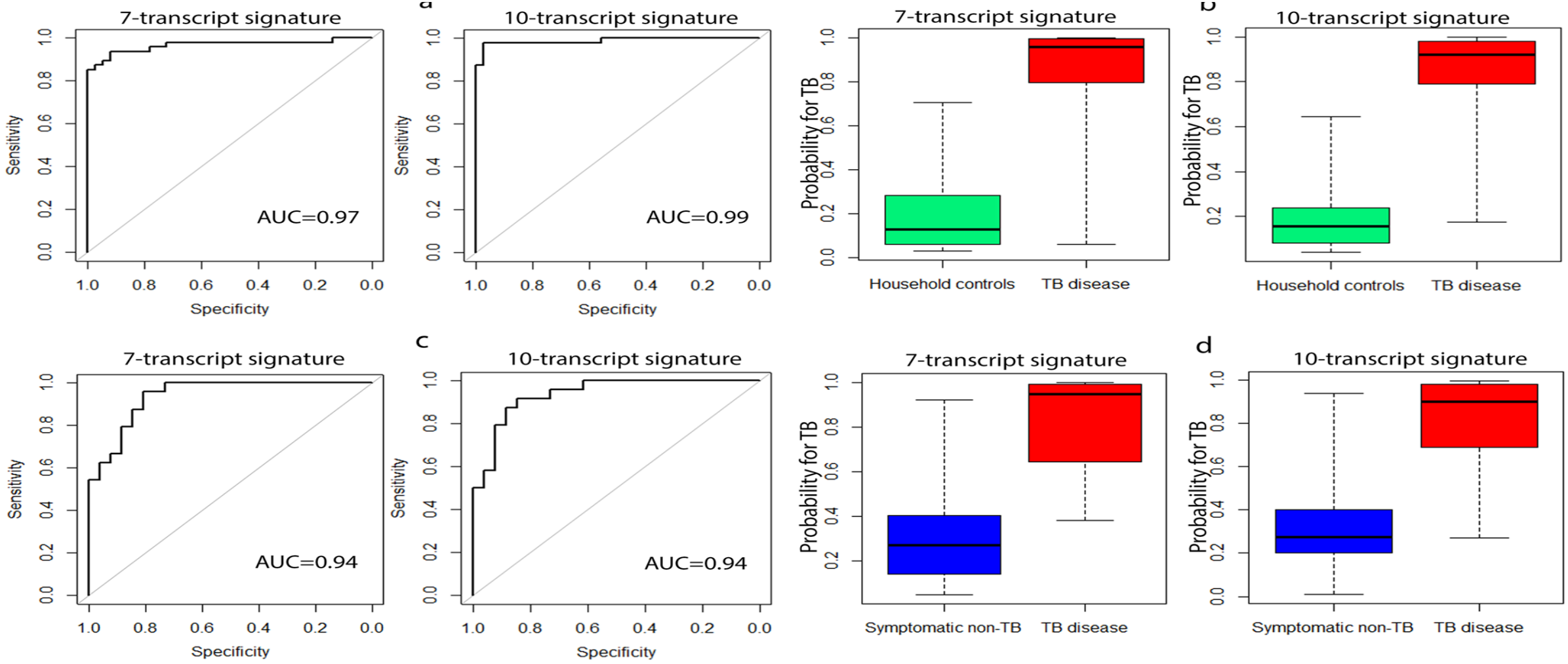


(Intercept)	23.465582802
Age	0.010245474
BPI	0.012292786
CCR7	0.178075846
FCGR1A	-0.827460880
CD14	-0.359563796
SEC14L1	-0.467106340
MMP9	-0.095198721
TIMP2	-2.131942583
TGFBR2	1.733767930

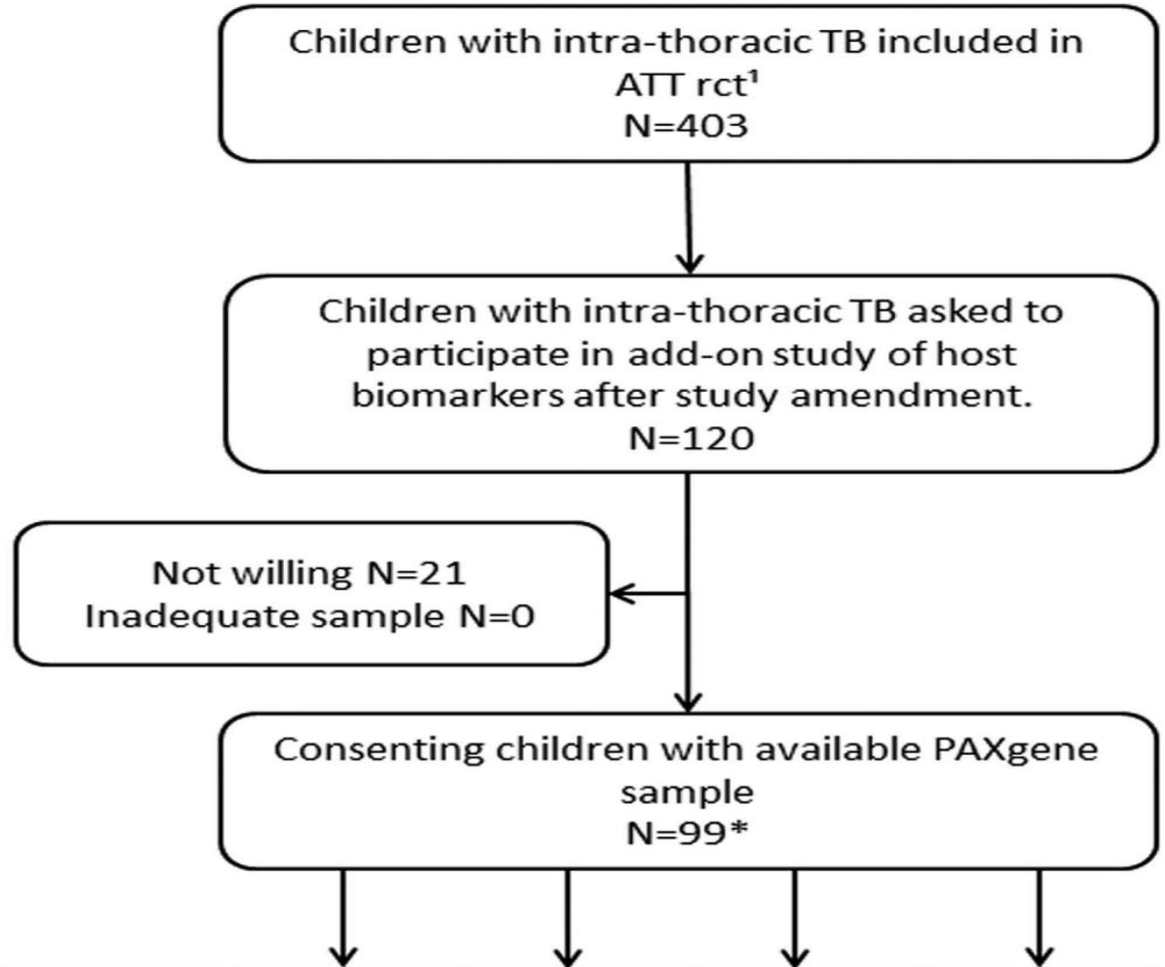




Novel Transcriptional Diagnostic Biomarkers

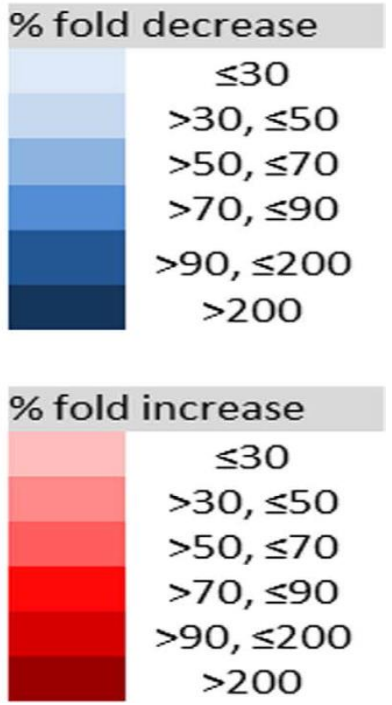


Sci Rep. 2017 Jul 19;7(1):5839.



	MN+Zn[1] (n)	MN[1] (n)	Zn[1] (n)	Placebo[1] (n)
Baseline	23	18	23	24
2 months	13	15	18	19
6 months	5	1	2	2

	MN+Zn	MN	Zn	Placebo
N baseline	23	18	23	24
N 2 months	13	15	18	19
BCL2	1,79 (1,36-2,34)	1,77 (1,36-2,29)	1,54 (1,22-1,94)	1,9 (1,51-2,38)
BLR1	2,63 (1,60-4,31)	1,94 (1,20-3,14)	2,26 (1,47-3,46)	1,97 (1,29-3,00)
CASP8	1,46 (1,21-1,76)	1,11 (0,93-1,33)	1,21 (1,03-1,42)	1,25 (1,07-1,47)
CD19	1,74 (1,22-2,48)	1,47 (1,00-2,16)	2,4 (1,73-3,33)	2,41 (1,75-3,30)
CD3E	1,93 (1,41-2,64)	2,01 (1,48-2,72)	1,76 (1,34-2,31)	1,96 (1,5-2,56)
CD4	1,46 (1,04-2,05)	1,43 (1,04-1,99)	1,79 (1,34-2,41)	1,47 (1,1-1,96)
FCGR1A	0,43 (0,29-0,63)	0,51 (0,35-0,75)	0,52 (0,37-0,72)	0,71 (0,51-0,99)
FPR1	0,63 (0,51-0,78)	0,74 (0,60-0,91)	0,78 (0,65-0,93)	0,76 (0,63-0,91)
IL7R	1,83 (1,41-2,36)	1,54 (1,20-1,99)	1,46 (1,17-1,82)	1,57 (1,26-1,96)
MMP9	0,25 (0,14-0,45)	0,55 (0,32-0,93)	0,44 (0,26-0,74)	0,22 (0,13-0,37)
TGFBR2	1,51 (1,26-1,81)	1,26 (1,06-1,50)	1,38 (1,18-1,62)	1,2 (1,03-1,40)



Sci Rep. 2016 Dec 12;6:38841.

Transcryptom and Outcome

BM change with treatment	BM entered in the model	Smear positivity[c]		*Mtb* culture positive[c]		Cavitating disease		Body Mass Index Z-score < −2		Body Mass Index Z-score, continous scale		Association with treatment outcomes	
		OR	95% CI for OR	OR	95% CI for OR	OR	95% CI for OR	OR	95% CI for OR	Rho	p	2 months	6 months
	FCGR1A	ns		3,14	(1,584–6,21)	ns		ns		ns		YES[a]	YES[a]
Decrease	*FPR1*	9,78	(2,09–45,8)	ns		ns		2,83	(1,13–7,14)	ns		ns	ns
	MMP9	ns		1,44	(1,02–2,03)	1,82	(1,06–3,12)	ns		−0,24	0,024	ns	ns
	BCL2	0,3	(0,1–0,92)	ns		0,12	(0,03–0,49)	ns		ns		ns	ns
	BLR1	0,47	(0,32–0,70)	0,46	(0,28–0,74)	0,5	(0,33–0,74)	ns		0,24	0,026	YES[b]	ns
Increase	*CASP8*	ns		ns		0,13	(0,03–0,68)	ns		ns		ns	ns
	CD3E	0,42	(0,23–0,78)	0,55	(0,33–0,92)	0,38	(0,20–0,75)	ns		0,23	0,037	ns	ns
	CD4	0,37	(0,18–0,78)	ns		0,45	(0,23–0,88)	ns		ns		ns	ns
	CD19	ns		ns		ns		ns		0,22	0,043	ns	ns
	IL7R	0,25	(0,11–0,56)	0,38	(0,21–0,69)	0,22	(0,09–0,53)	ns		0,22	0,04	ns	ns
	TGFBR2	0,22	(0,05–0,94)	0,11	(0,03–0,37)	0,02	(0,003–0,19)	ns		ns		ns	ns

Sci Rep. 2016 Dec 12;6:38841.

Meta analysis

- Studies were included if they:
  - Assessed the accuracy of Xpert MTB/RIF Ultra for diagnosis of TB
  - had a well defined reference standard for TB
  - provided sufficient information to construct the 2 by 2 contingency table—i.e., false and true positives and negatives were provided.
- Studies were not restricted on age of study population (adults or children), specimen type (respiratory or extrapulmonary samples), settings and countries

Exclusion Criteria

- Animal experiments, reviews, correspondences, commentaries, interim analyses, case reports and editorials were excluded