Bacterial and host determinants of cough aerosol culture-positivity in patients with tuberculosis diagnosed during community based active case finding

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BACKGROUND

TB top ID killer- 3 people die every minute! Over 1 billion people killed over the last 2 centuries!

Preventing the spread of TB, which mainly occurs via coughing, is critical to reducing the burden of TB disease.

However, we must first identify those that are most at risk for transmitting the disease; also known as ‘super-spreaders’.

35% of TB patients remain undetected globally and up to 50% of these do not show any symptoms of TB → large reservoir of TB ‘super-spreaders’ present in the community that perpetuates amplification of the TB epidemic.

BACKGROUND

CHALLENGE: we cannot accurately identify the infectious persons or super-spreaders.

PROPOSAL: a test or biosignature to identify such persons to:

(i) rapidly identify and target them for interventions including tracing their close contacts more intensively.

(ii) enable us to study and perform a root cause analysis of transmission (not currently possible as we cannot identify the highly infectious cases).

AIMS

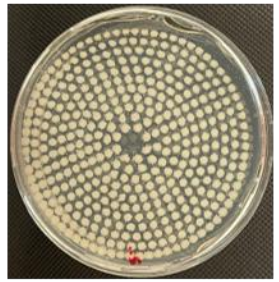
Aim 1: Investigating M.tb specific factors (genomic, epigenetic, microbiological) associated with infectiousness

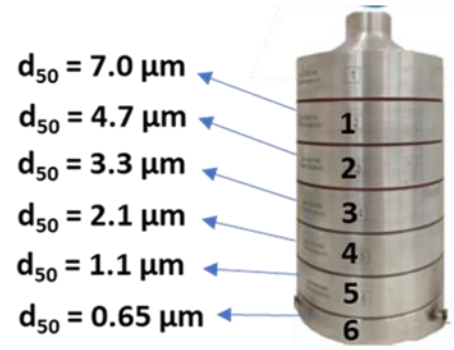
Aim 2: Correlation of host-specific biomarkers (blood, urine, sputum clinical and imaging) with infectiousness

Aim 3: Development of a user-friendly combinatorial biosignature/score for infectiousness leveraging read-outs from Aims 1 & 2

CLINICAL METHODOLOGY

Brooklyn Chest Hospital – CASS Procedure

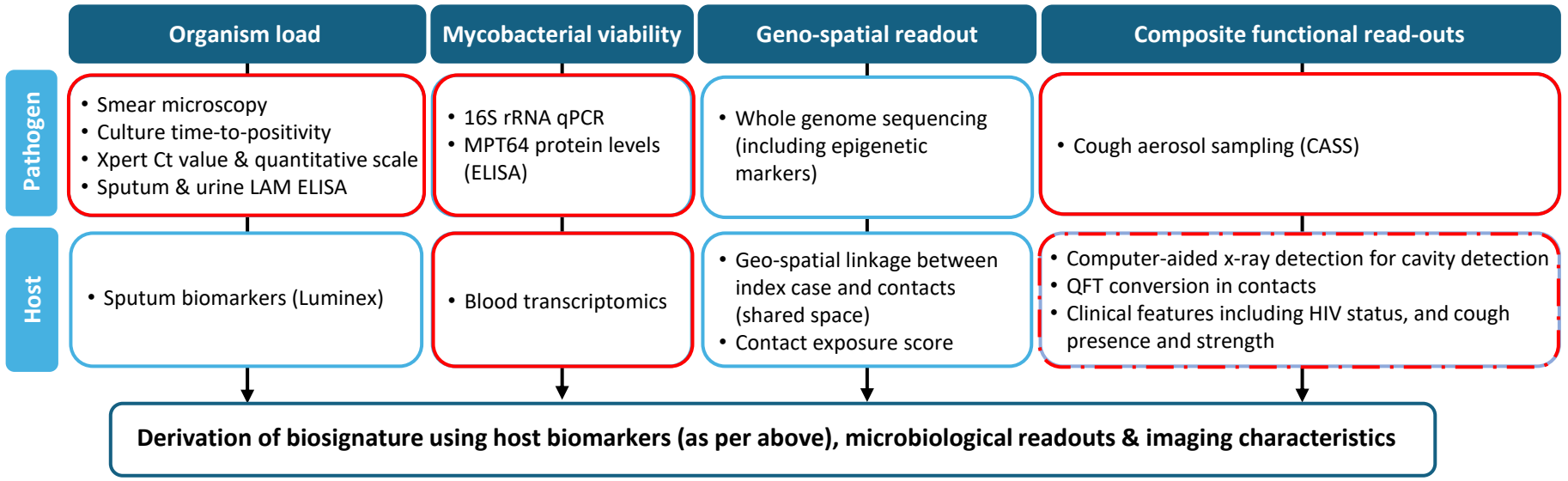




d50 = stage-specific median particle diameter

SCIENTIFIC METHODOLOGY

	XACT-2	XACT-3	XACT-19	TOTAL
Screened	5274	3374	6000	14648
Diagnosed	584	843	1500	2927
CASSed	31	86	58	175



RESULTS

HOST CHARACTERISTICS

Characteristics	Total	CASS+	CASS-	Odds Ratio (95% CI)	p-value
n	175	23	152		
Median age (IQR)	38 (30-47)	32 (28-43)	38 (32-48)	0.96 (0.92-1.00)	0.05
Gender					
Male	84 (48)	14 (61)	70 (46)	1.82 (0.74-4.46)	0.26
Female	91 (52)	9 (39)	82 (54)		
BMI					
Normal	115 (66)	15 (65)	100 (66)		
Underweight	36 (21)	6 (26)	30 (20)	0.75 (0.27-2.10)	0.59
Overweight	17 (10)	2 (9)	15 (10)	1.13 (0.23-5.42)	1.00
Obese	7 (3)	0 (0)	7 (4)	2.31 (0.13-42.59)	0.60
HIV status					
Positive	58 (33)	8 (35)	50 (33)	1.09 (0.43-2.74)	1.00
Negative	117 (67)	15 (65)	102 (67)		
Median blood CD4 count/mm^3 (IQR)	424 (265–605)	407 (265–611)	434 (262–605)	1.05 (0.78-3.41)	1.00
Smoking					
Yes	135 (77)	22 (96)	113 (74)	7.59 (0.99-58.24)	**0.03**
No	40 (23)	1 (4)	39 (26)		
Past history of TB					
Yes	115 (66)	15 (65)	100 (66)	0.98 (0.39-2.45)	1.00
No	60 (34)	8 (35)	52 (34)		
Chest X-ray with cavitary findings					
Yes	74 (45)	11 (52)	63 (44)	1.41 (0.56-3.54)	0.49
No	91 (55)	10 (48)	81 (56)		
Symptomatic					
Yes	86 (49)	19 (83)	67 (44)	6.03 (1.96-18.56)	**0.0006**
No	89 (51)	4 (17)	85 (56)		
Cough	79	18 (78)	61 (40)	5.37 (1.89-15.24)	**0.0007**
Hemoptysis	4	1 (4)	3 (2)	2.26 (0.22-22.69)	0.43
Pleuritic chest pain	33	9 (39)	24 (16)	3.43 (1.33-8.82)	**0.02**
Shortness of breath*	17	1 (4)	16 (13)	0.30 (0.04-2.37)	0.31
Fever	17	3 (13)	14 (9)	1.48 (0.39-5.61)	0.47
Loss of appetite	41	11 (48)	30 (20)	3.73 (1.50-9.27)	**0.007**
Weight loss	56	12 (52)	44 (29)	2.68 (1.10-6.52)	**0.03**
Night sweats	54	11 (48)	43 (28)	2.32 (0.95-5.67)	0.09
Fatigue/Lethargy	49	10 (43)	39 (26)	2.23 (0.90-5.49)	0.09

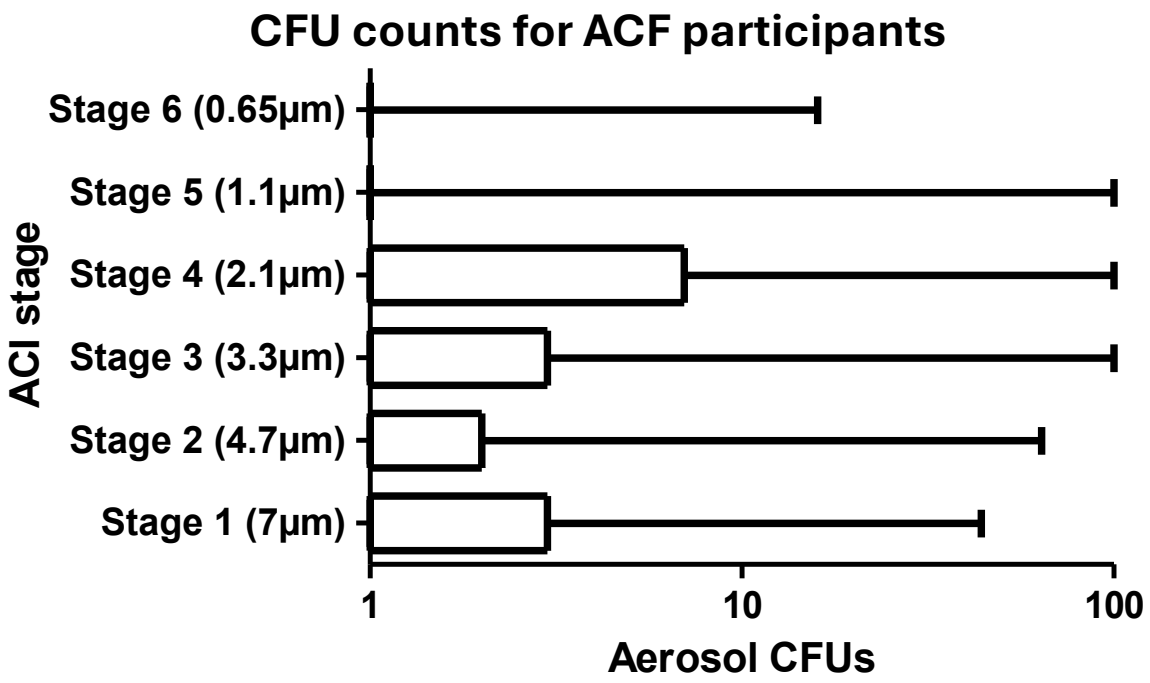
RESULTS

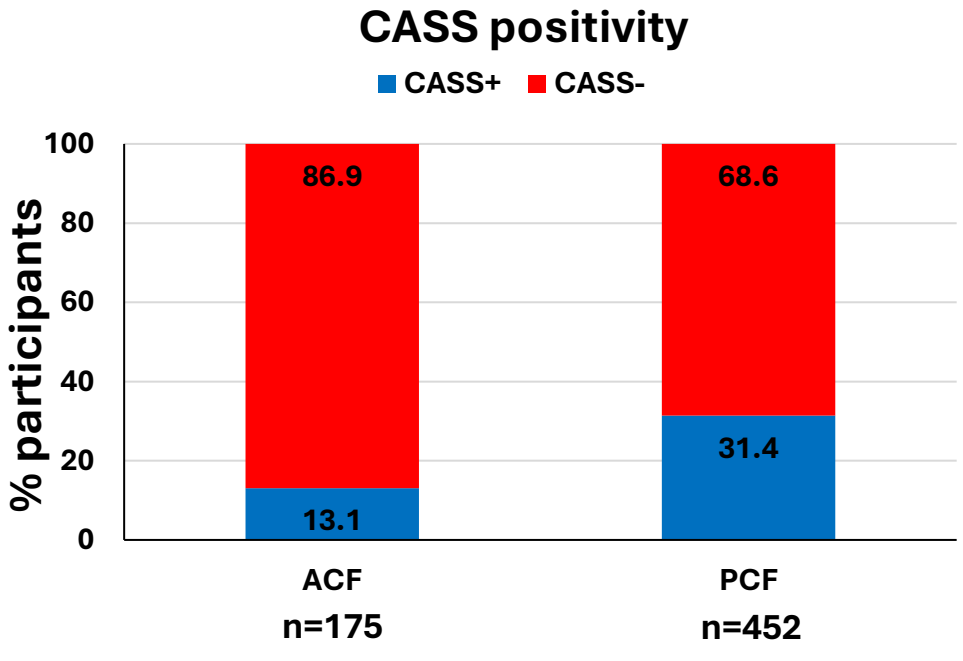
MICROBIOLOGICAL CHARACTERISTICS

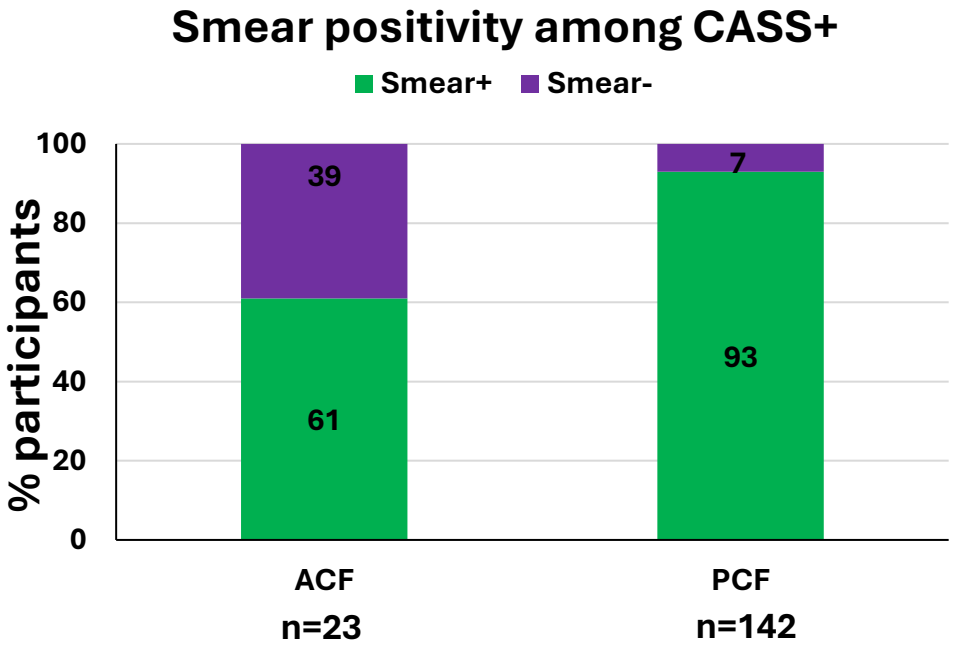
Characteristics	Total	CASS+	CASS-	Odds Ratio (95% CI)	p-value
n	175	23	152		
Smear positive	23 (13)	14 (61)	9 (6)	24.54 (8.38-71.91)	**<0.0001**
Scanty	2 (1)	2 (9)	0	-	-
Grade 1	4 (2)	0 (0)	4 (3)	-	-
Grade 2	6 (3)	4 (17)	2 (1)	-	-
Grade 3	11 (6)	8 (35)	3 (2)	-	-
Xpert positive	119 (76)	18 (100)	101 (73)	14.03 (0.82-238.8)	**0.007**
Trace	26 (17)	0 (0)	26 (19)	-	-
Very low	20 (13)	0 (0)	20 (14)	-	-
Low	34 (22)	2 (11)	32 (23)	-	-
Medium	11(7)	6 (33)	5 (4)	-	-
High	12 (8)	7 (39)	5 (4)	-	-
Unknown	16 (10)	3 (17)	13 (9)	-	-
Median Xpert Ct	26 (21-29)	20 (18-21)	28 (24-31)	0.63 (0.50-0.81)	**<0.0001**

RESULTS

CASS FINDINGS:
ACF (n=175) VERSUS
PCF (n=452)





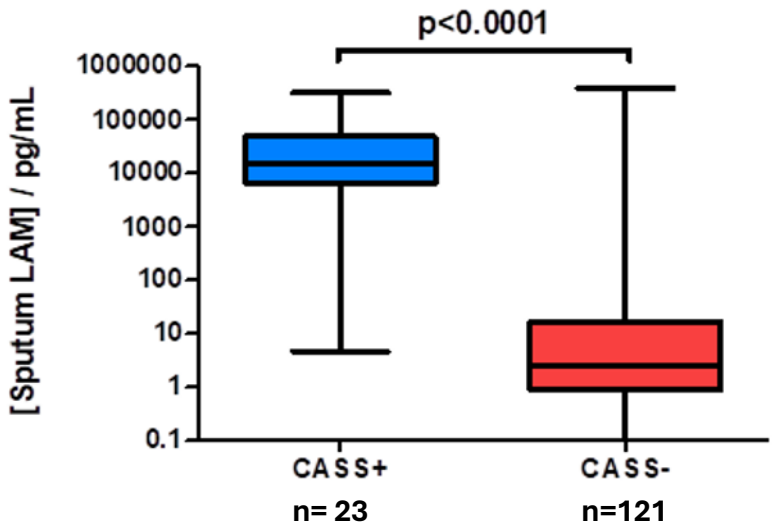


RESULTS

PATHFAST TB
SPUTUM LAM Ag

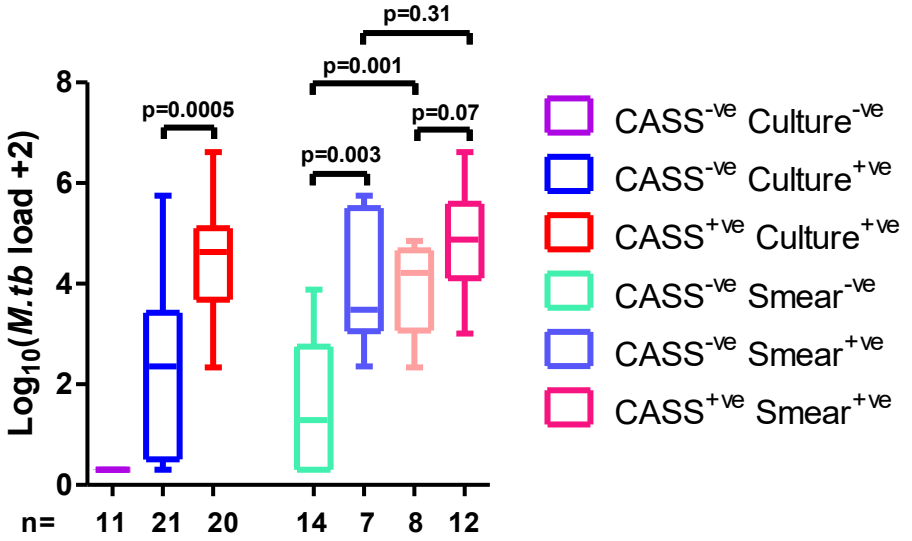
MBLA 16SrRNA

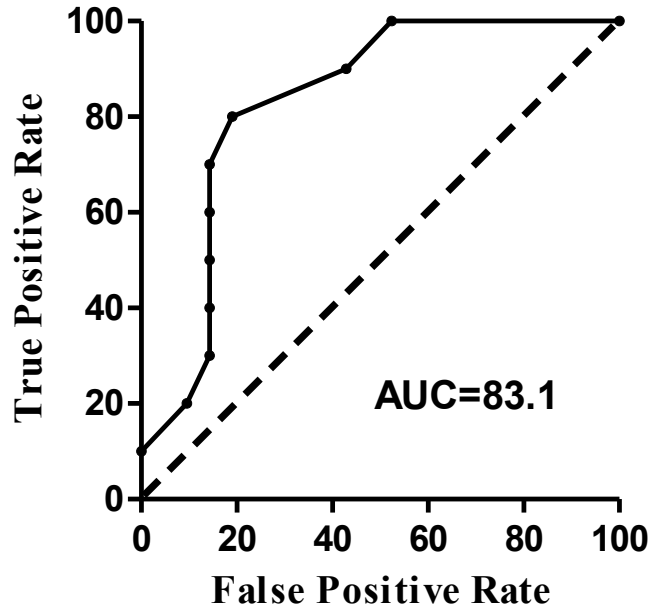
PATHFAST LAM Ag



Sensitivity	Specificity	Cut-off
100	55.8	3.11
95	62.5	4.68
90	87.5	228
85	90.8	427
80	92.5	3579
75	94.1	6623

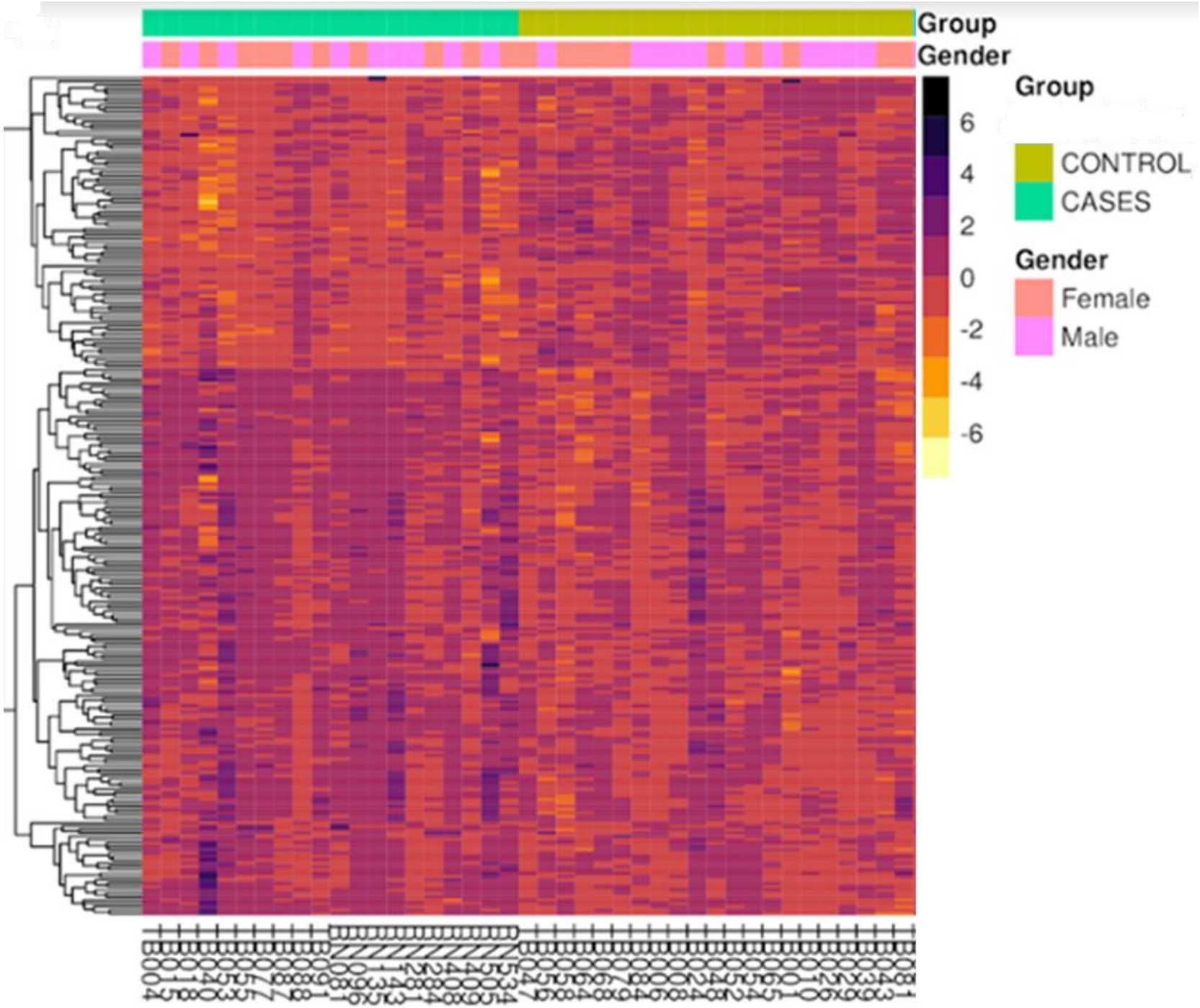
MBLA 16S rRNA





RESULTS

Blood transcriptomic signatures in CASS+ probably infectious individuals (n=20) versus CASS- individuals (n=21)



SUMMARY

TB transmission in the community remains poorly understood.

Rapid identification of infectious cases would also allow their rapid isolation (especially in difficult to treat drug-resistant TB cases) and in hospitalised patients where isolation type facilities are often limited.

Our study expands on the relatively novel concept of developing a biosignature predictive of TB infectiousness.

Our work has revealed 4 biomarkers predictive of cough aerosol positivity:

- Xpert Ct value
- PATHFAST sputum LAM
- 16S rRNA
- Blood based transcriptomic profile

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