Prospective multicentre head-to-head validation of host blood transcriptomic biomarkers for pulmonary tuberculosis by real-time PCR

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SUPPLEMENTARY INFORMATION

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Supplementary Notes 1

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Supplementary Notes 2

Signature failure rate

Although different pass rates may have biased comparison of performance between signature, the primary aim of the study was to compare individual signature performance to the WHO Target Product Profile (TPP) criteria benchmarks rather than against each other. Hence samples with failed signatures were still included in analysis to increase statistical power. Failure rate is also an indicator of signature robustness; an important criterion when selecting biomarkers for further development and clinical translation. The high failure rate of the Suliman4 signature was attributed to the GAS6 primer-probe assay, which performed well in assay qualification (**Table S3 in Supplementary Data 1**) and validation in high yield and purity manually extracted PAXgene RNA samples. However, performance of the GAS6 assay was less robust in lower yield and quality RNA from automated robotic extraction in the CORTIS studies. Due to the pair-wise ensemble structure of three up- and three down-regulated genes, RISK6 score can still be calculated even if one or more transcript is not detected due to failed PCR amplification.[1] As a result, RISK6 was resilient to single failed PCR reactions, with highest signature pass rate. Only HIV-uninfected participants with successful measurement of the RISK11 score were enrolled in the CORTIS-01 study, whereas HIV-infected participants were enrolled irrespective of RISK11 score in CORTIS-HR. This effectively excluded participants in CORTIS-01 with very low yield or purity RNA samples, resulting in a lower signature failure rates in CORTIS-01 as compared to CORTIS-HR.

Supplementary Figures

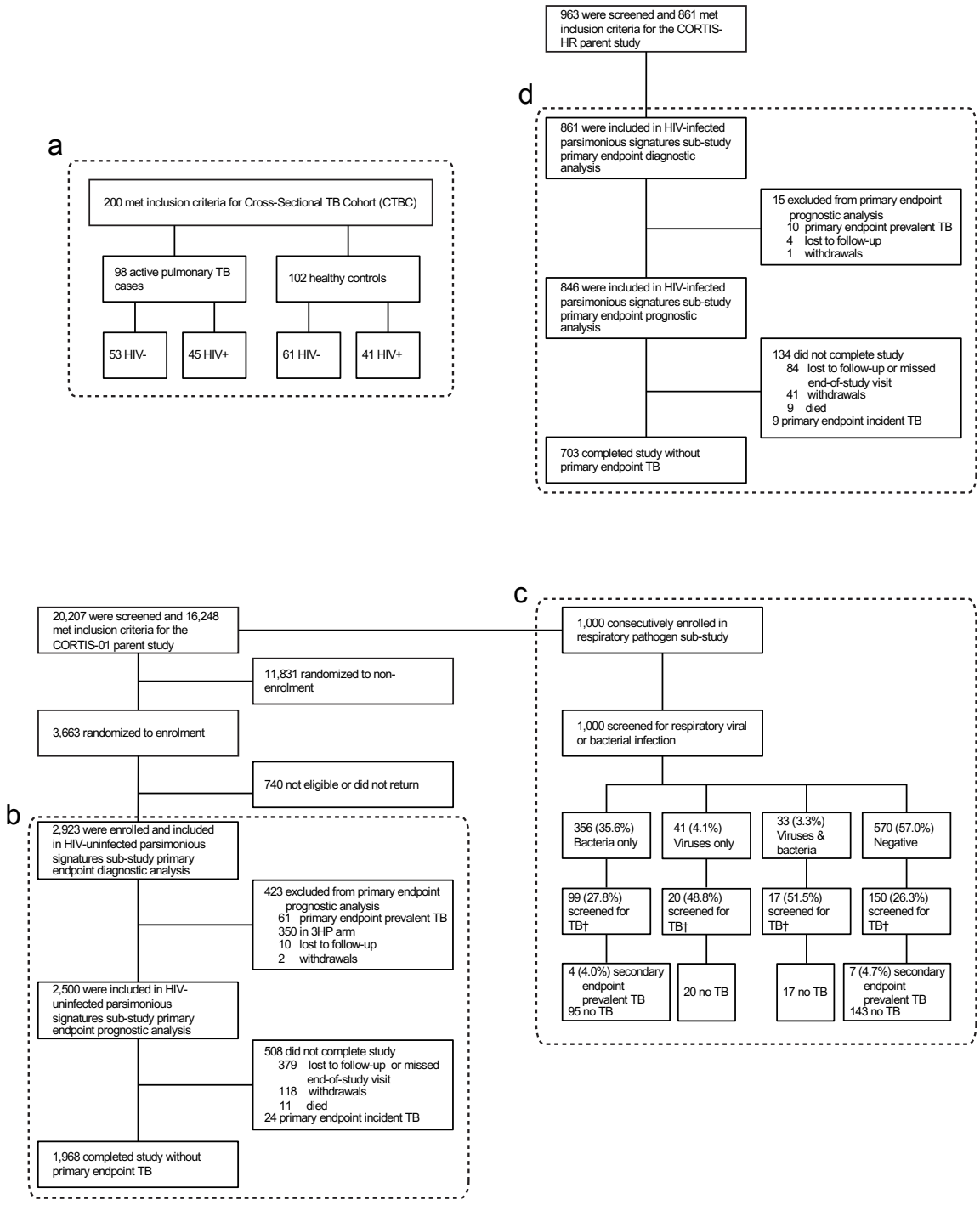

Figure S1: Study flow diagram

(a) HIV-infected and HIV-uninfected participants with and without TB were recruited into the Cross-Sectional TB Cohort (CTBC) case-control study. HIV-uninfected participants were recruited from the CORTIS-01 parent study and co-enrolled into the (b) HIV-uninfected parsimonious signatures sub-study and (c) respiratory pathobionts sub-study. HIV-infected participants were recruited from the CORTIS-HR parent study and co-enrolled into the (d) HIV-infected parsimonious signatures sub-study. For the CTBC study and respiratory pathobionts sub-study, TB disease was defined by a single sputum sample positive for *Mtb* on either Xpert MTB/RIF and/or liquid culture at enrolment. The coprimary endpoints in the CORTIS studies were baseline prevalent TB disease and incident disease through 15 months follow-up confirmed by a positive Xpert MTB/RIF, Xpert Ultra, or MGIT culture, on two or more separate sputum samples collected within any 30-day period. The secondary endpoint was microbiologically-confirmed TB disease on at least one sputum sample.

†Out of 1000 participants enrolled in the respiratory pathobionts cohort, only 286 (28.6%) participants were co-enrolled in the CORTIS-01 parent study and investigated for TB at enrolment; 11/286 (3.8%) had prevalent TB confirmed by *Mycobacterium tuberculosis* liquid culture and/or Xpert MTB/RIF.

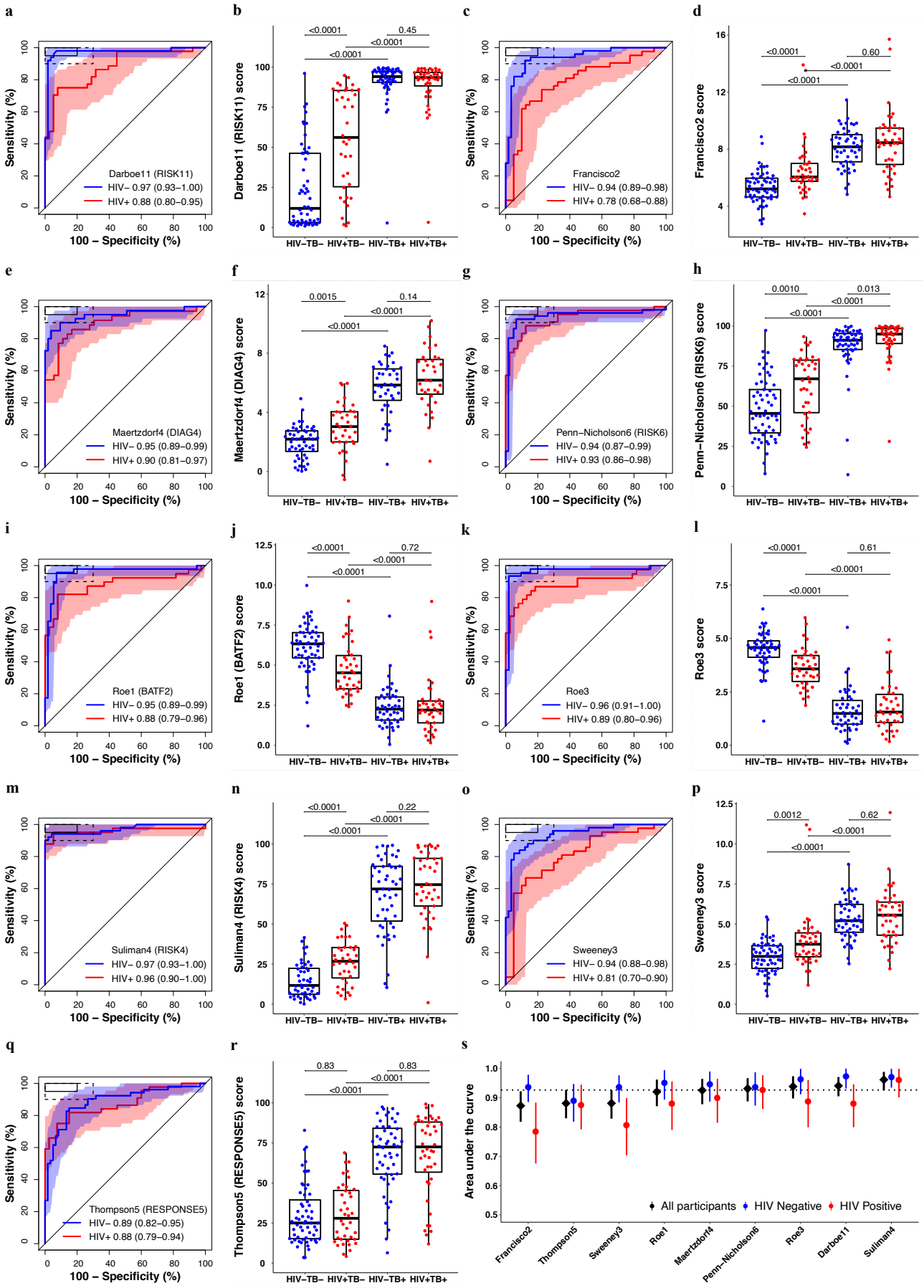
a
Sensitivity (%)
100 – Specificity (%)
Darboe11 (RISK11)
HIV– 0.97 (0.93–1.00)
HIV+ 0.88 (0.80–0.95)
b
Darboe11 (RISK11) score
<0.0001
0.45
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
c
Sensitivity (%)
100 – Specificity (%)
Francisco2
HIV– 0.94 (0.89–0.98)
HIV+ 0.78 (0.68–0.88)
d
Francisco2 score
<0.0001
0.60
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
e
Sensitivity (%)
100 – Specificity (%)
Maertzdorf4 (DIAG4)
HIV– 0.95 (0.89–0.99)
HIV+ 0.90 (0.81–0.97)
f
Maertzdorf4 (DIAG4) score
0.0015
0.14
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
g
Sensitivity (%)
100 – Specificity (%)
Penn–Nicholson6 (RISK6)
HIV– 0.94 (0.87–0.99)
HIV+ 0.93 (0.86–0.98)
h
Penn–Nicholson6 (RISK6) score
0.0010
0.013
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
i
Sensitivity (%)
100 – Specificity (%)
Roe1 (BATF2)
HIV– 0.95 (0.89–0.99)
HIV+ 0.88 (0.79–0.96)
j
Roe1 (BATF2) score
<0.0001
0.72
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
k
Sensitivity (%)
100 – Specificity (%)
Roe3
HIV– 0.96 (0.91–1.00)
HIV+ 0.89 (0.80–0.96)
l
Roe3 score
<0.0001
0.61
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
m
Sensitivity (%)
100 – Specificity (%)
Suliman4 (RISK4)
HIV– 0.97 (0.93–1.00)
HIV+ 0.96 (0.90–1.00)
n
Suliman4 (RISK4) score
<0.0001
0.22
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
o
Sensitivity (%)
100 – Specificity (%)
Sweeney3
HIV– 0.94 (0.88–0.98)
HIV+ 0.81 (0.70–0.90)
p
Sweeney3 score
0.0012
0.62
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
q
Sensitivity (%)
100 – Specificity (%)
Thompson5 (RESPONSE5)
HIV– 0.89 (0.82–0.95)
HIV+ 0.88 (0.79–0.94)
r
Thompson5 (RESPONSE5) score
0.83
0.83
<0.0001
<0.0001
HIV–TB– HIV+TB– HIV–TB+ HIV+TB+
s
Area under the curve
All participants
HIV Negative
HIV Positive
Francisco2
Thompson5
Sweeney3
Roe1
Maertzdorf4
Penn–Nicholson6
Roe3
Darboe11
Suliman4

Figure S2: Parsimonious signatures diagnostic performance and signature score distributions in the Cross-sectional Tuberculosis Cohort (CTBC) study

Paired receiver operating characteristic (ROC) curves and box-and-whisker plots for the (a-b) Darboe11 (RISK11), (c-d) Francisco2, (e-f) Maertzdorf4 (DIAG4), (g-h) Penn-Nicholson6 (RISK6), (i-j) Roe1 (BATF2), (k-l) Roe3, (m-n) Suliman4 (RISK4), (o-p) Sweeney3, and (Q-R) Thompson5 (RESPONSE5) signatures in the Cross-sectional Tuberculosis Cohort (CTBC) study.

The ROC curves depict diagnostic performance (area under the curve, AUC, with 95% CI) of the parsimonious signatures for diagnosing TB, stratified by HIV status. The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2]

The box-and-whisker plots depict signature score distribution by HIV (HIV+/HIV-) and prevalent TB disease (TB+/TB-) status. Each dot represents a participant. p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR).

(S) Summary of signature diagnostic performance in order of AUC estimates in all participants. The diagnostic AUC estimates in HIV-infected and HIV-uninfected participant sub-groups are also shown. The midline indicates the AUC estimate, the error bars indicate the 95% CIs, and the black dotted line indicates the lower bound of the 95% CI for the best performing signature for all participants.

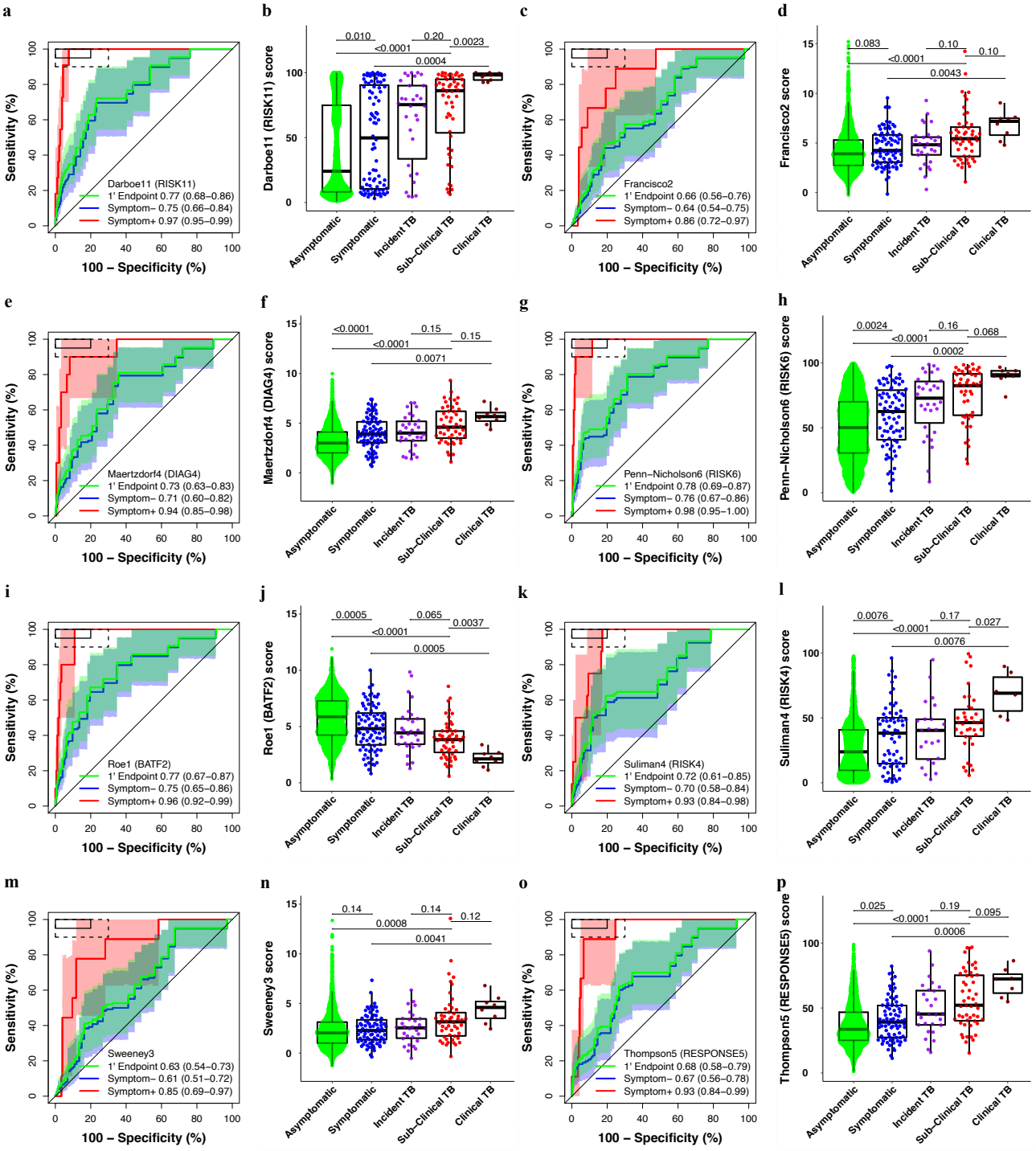

Figure S3: Parsimonious signature diagnostic performance for prevalent TB and signature score distributions in people without HIV

Paired receiver operating characteristic (ROC) curves and box-and-whisker plots for the (a-b) Darboe11 (RISK11), (c-d) Francisco2, (e-f) Maertzdorf4 (DIAG4), (g-h) Penn-Nicholson6 (RISK6), (i-j) Roe1 (BATF2), (k-l) Suliman4 (RISK4), (m-n) Sweeney3, and (o-p) Thompson5 (RESPONSE5) signatures in the CORTIS-01 study of people without HIV. The ROC curves depict diagnostic performance (area under the curve, AUC, with 95% CI) of the parsimonious signatures for the primary endpoint (1' Endpoint), i.e. TB diagnosed on two or more liquid culture-positive or Xpert MTB/RIF-positive sputum samples. The ROC curves show participants with symptomatic clinical prevalent TB versus symptomatic controls (Symptom+), and participants with asymptomatic, subclinical prevalent TB versus asymptomatic controls (Symptom–). The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2] The box-and-whisker plots depict signature score (measured at enrolment) distribution by symptom status (each dot represents a participant) in asymptomatic and symptomatic participants with no TB, participants who progressed to incident TB, and participants with prevalent subclinical (asymptomatic) and clinical (symptomatic) TB. Prevalent and incident TB comprised all primary endpoint cases. Symptoms were recorded at the time of enrolment for participants without TB and those with prevalent TB. p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR).

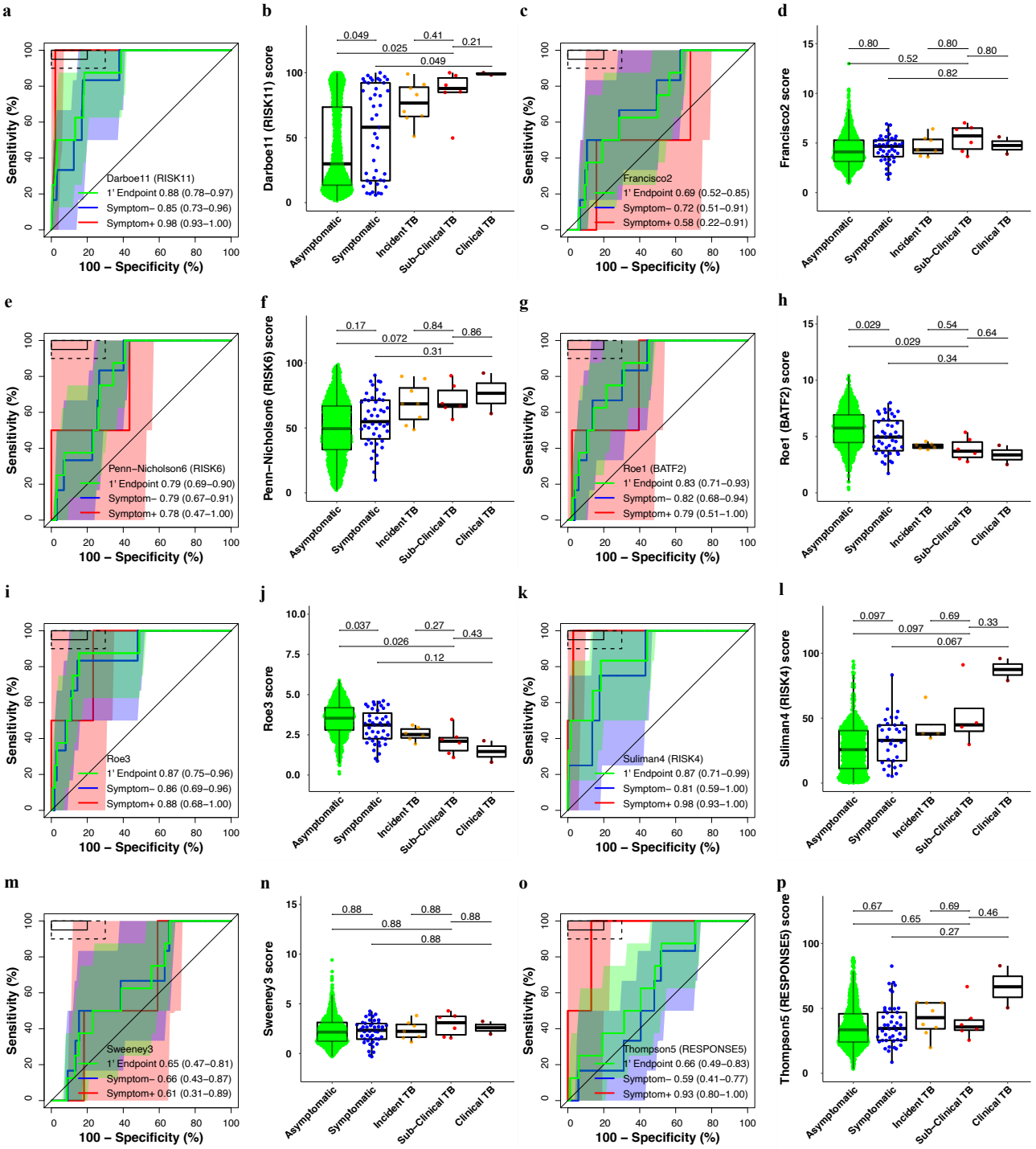

Figure S4: Parsimonious signatures diagnostic performance for prevalent TB and signature score distributions in people living with HIV. Paired receiver operating characteristic (ROC) curves and box-and-whisker plots for the (a-b) Darboe11 (RISK11), (c-d) Francisco2, (e-f) Penn-Nicholson6 (RISK6), (g-h) Roe1 (BATF2), (i-j) Roe3, (k-l) Suliman4 (RISK4), (m-n) Sweeney3, and (o-p) Thompson5 (RESPONSE5) signatures in the CORTIS-HR study of people living with HIV. The ROC curves depict diagnostic performance (area under the curve, AUC, with 95% CI) of the parsimonious signatures for TB diagnosed for the primary endpoint (1' Endpoint), i.e. TB diagnosed on two or more liquid culture-positive or Xpert MTB/RIF-positive sputum samples. The ROC curves show participants with symptomatic clinical prevalent TB versus symptomatic controls (Symptom+), and participants with asymptomatic subclinical prevalent TB versus asymptomatic controls (Symptom–). The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2] The box-and-whisker plots depict signature score (measured at enrolment) distribution by symptom status (each dot represents a participant) in asymptomatic and symptomatic participants with no TB, participants who progressed to incident TB, and participants with prevalent subclinical (asymptomatic) and clinical (symptomatic) TB. Prevalent and incident TB comprised all primary endpoint cases. Symptoms were recorded at the time of enrolment for participants without TB and those with prevalent TB. p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR).

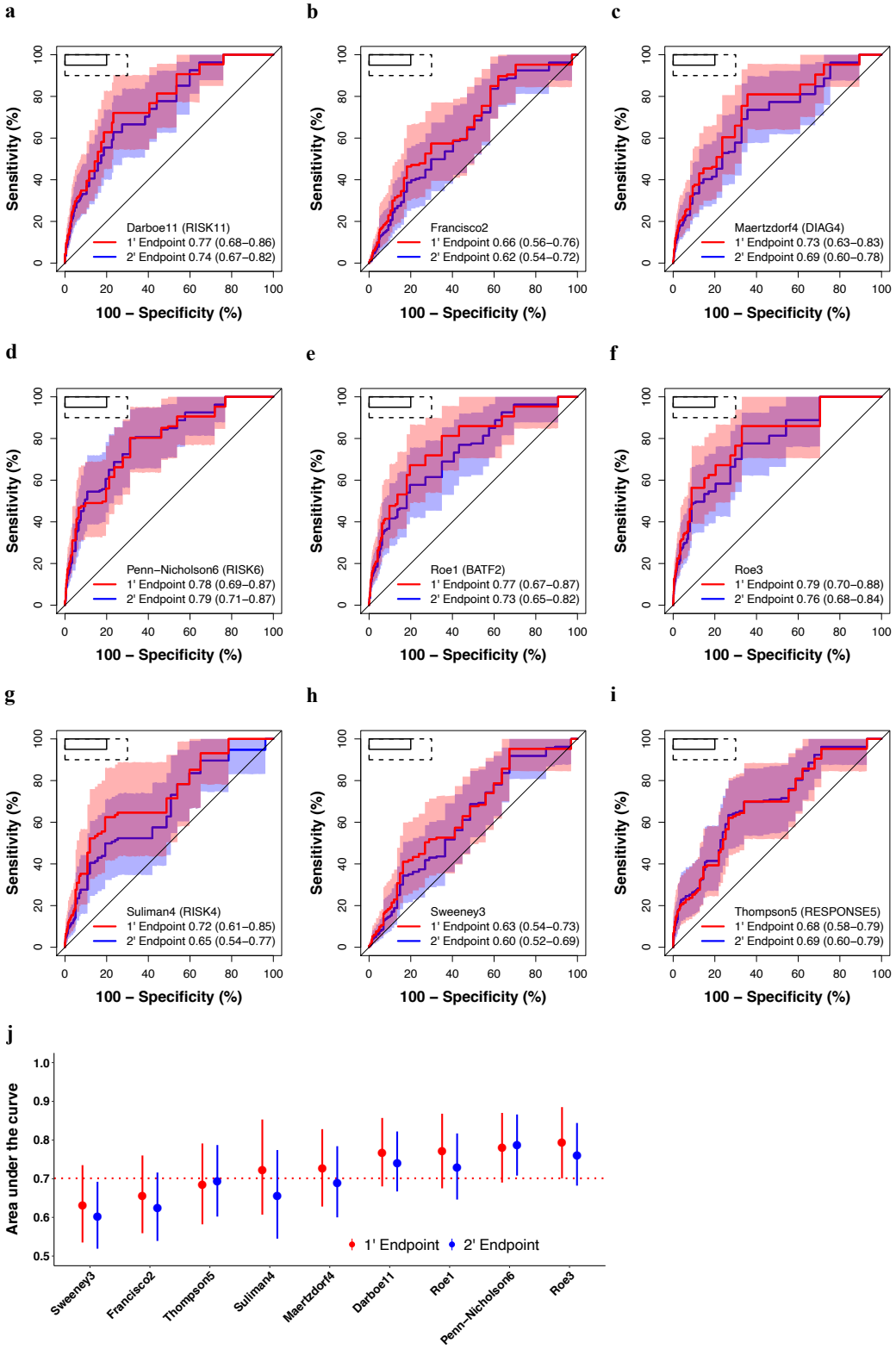

Figure S5: Parsimonious signatures diagnostic performance for primary versus secondary endpoint TB in people without HIV

Receiver operating characteristic (ROC) curves depicting primary ('1) versus secondary ('2) endpoint diagnostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Penn-Nicholson6 (RISK6), (e) Roe1 (BATF2), (f) Roe3, (g) Suliman4 (RISK4), (h) Sweeney3, and (i) Thompson5 (RESPONSE5) signatures in the CORTIS-01 study of people without HIV. The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2]

(j) Summary of signature diagnostic performance in order of primary endpoint AUC estimates. The diagnostic AUC estimates for the secondary endpoint are also shown. The midline indicates the AUC estimate, the error bars indicate the 95% CIs, and the red dotted line indicates the lower bound of the 95% CI for the best performing signature for the primary endpoint.

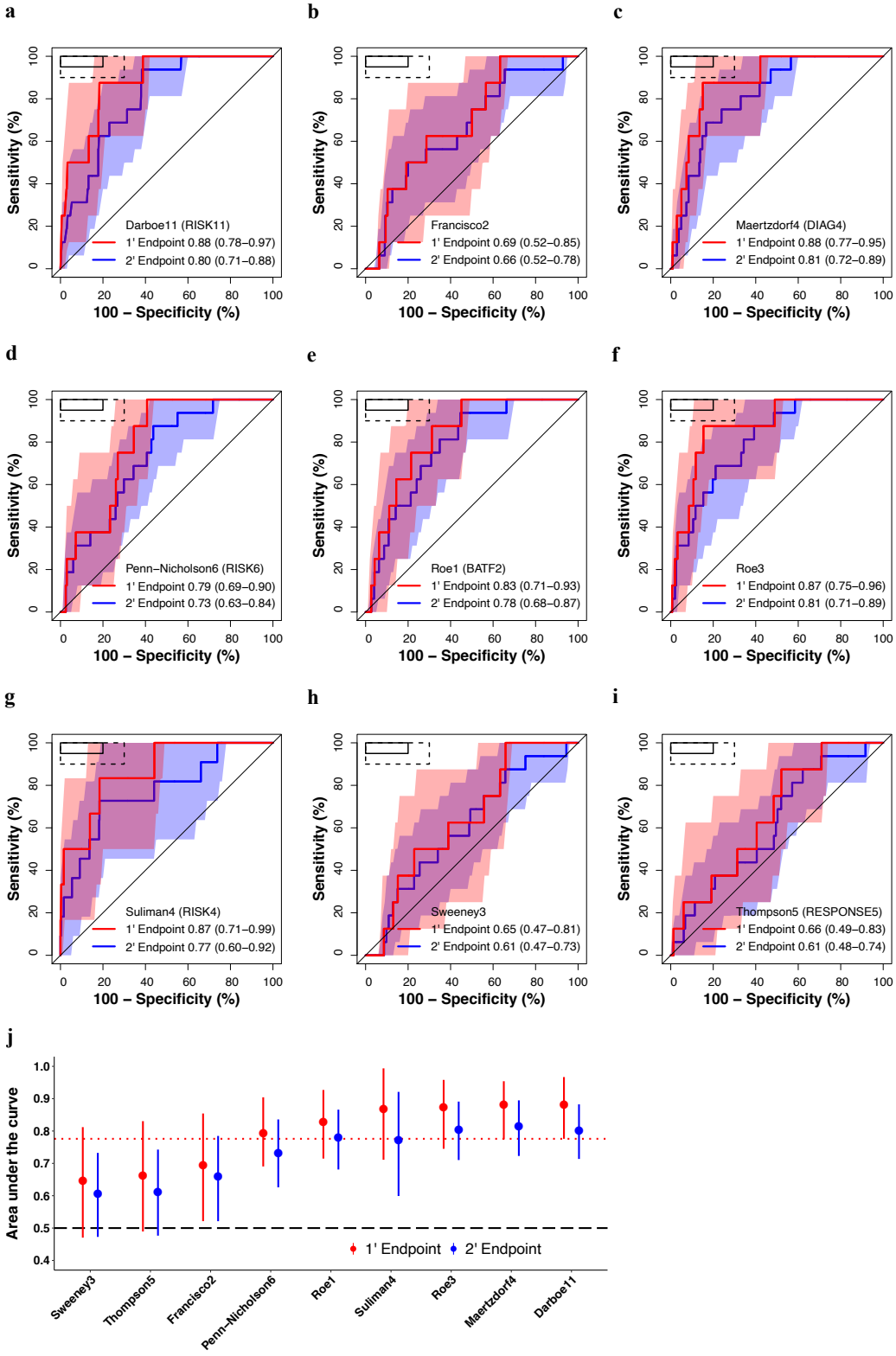

Figure S6: Parsimonious signatures diagnostic performance for primary versus secondary endpoint TB in people living with HIV

Receiver operating characteristic (ROC) curves depicting primary (‘1) versus secondary (‘2) endpoint diagnostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Penn-Nicholson6 (RISK6), (e) Roe1 (BATF2), (f) Roe3, (g) Suliman4 (RISK4), (h) Sweeney3, and (i) Thompson5 (RESPONSE5) signatures in the CORTIS-HR study of people living with HIV. The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2]

(j) Summary of signature diagnostic performance in order of primary endpoint AUC estimates. The diagnostic AUC estimates for the secondary endpoint are also shown. The midline indicates the AUC estimate, the error bars indicate the 95% CIs, and the red dotted line indicates the lower bound of the 95% CI for the best performing signature for the primary endpoint. The black dashed line indicates an AUC cut-off of 0.5.

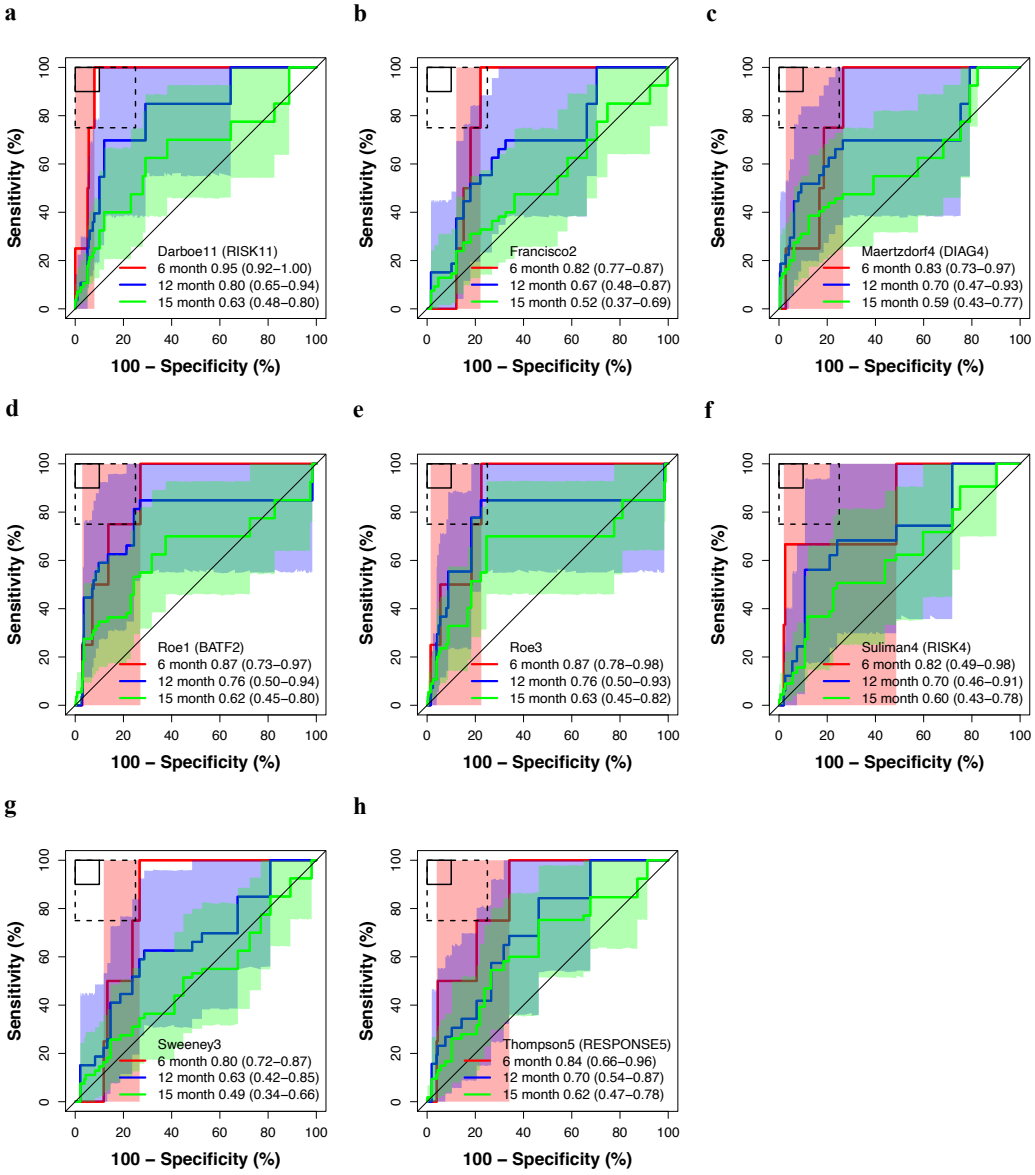

Figure S7: Parsimonious signature prognostic performance for incident TB in people without HIV

Receiver operating characteristic curves depicting prognostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Roe1 (BATF2), (e) Roe3, (f) Suliman4 (RISK4), (g) Sweeney3, and (h) Thompson5 (RESPONSE5) signatures for incident TB diagnosed on two or more liquid culture-positive or Xpert MTB/RIF-positive sputum samples (primary endpoint) through 6, 12, and 15 months follow-up in the CORTIS-01 study of people without HIV.

The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (90% sensitivity and 90% specificity) and the dashed box depicts the minimal criteria (75% sensitivity and 75% specificity) set out in the WHO Target Product Profile for an incipient TB test.[4]

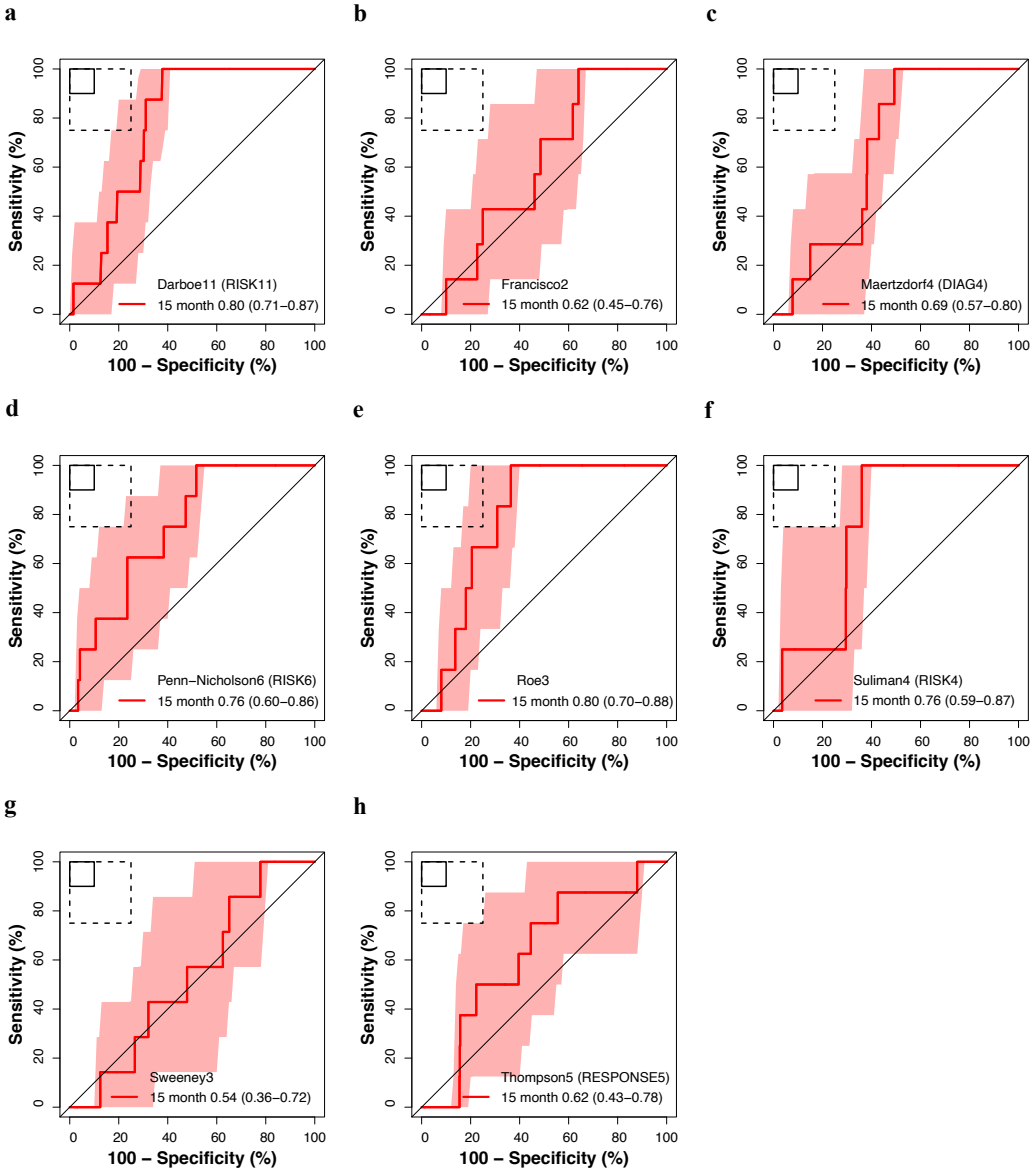

Figure S8: Parsimonious signature prognostic performance for prevalent TB in people living with HIV

Receiver operating characteristic curves depicting prognostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Penn-Nicholson6 (RISK6), (e) Roe3, (f) Suliman4 (RISK4), (g) Sweeney3, and (h) Thompson5 (RESPONSE5) signatures for incident TB diagnosed on two or more liquid culture-positive or Xpert MTB/RIF-positive sputum samples (primary endpoint) through 15 months follow-up in the CORTIS-HR study of people living with HIV.

The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (90% sensitivity and 90% specificity) and the dashed box depicts the minimal criteria (75% sensitivity and 75% specificity) set out in the WHO Target Product Profile for an incipient TB test.[4]

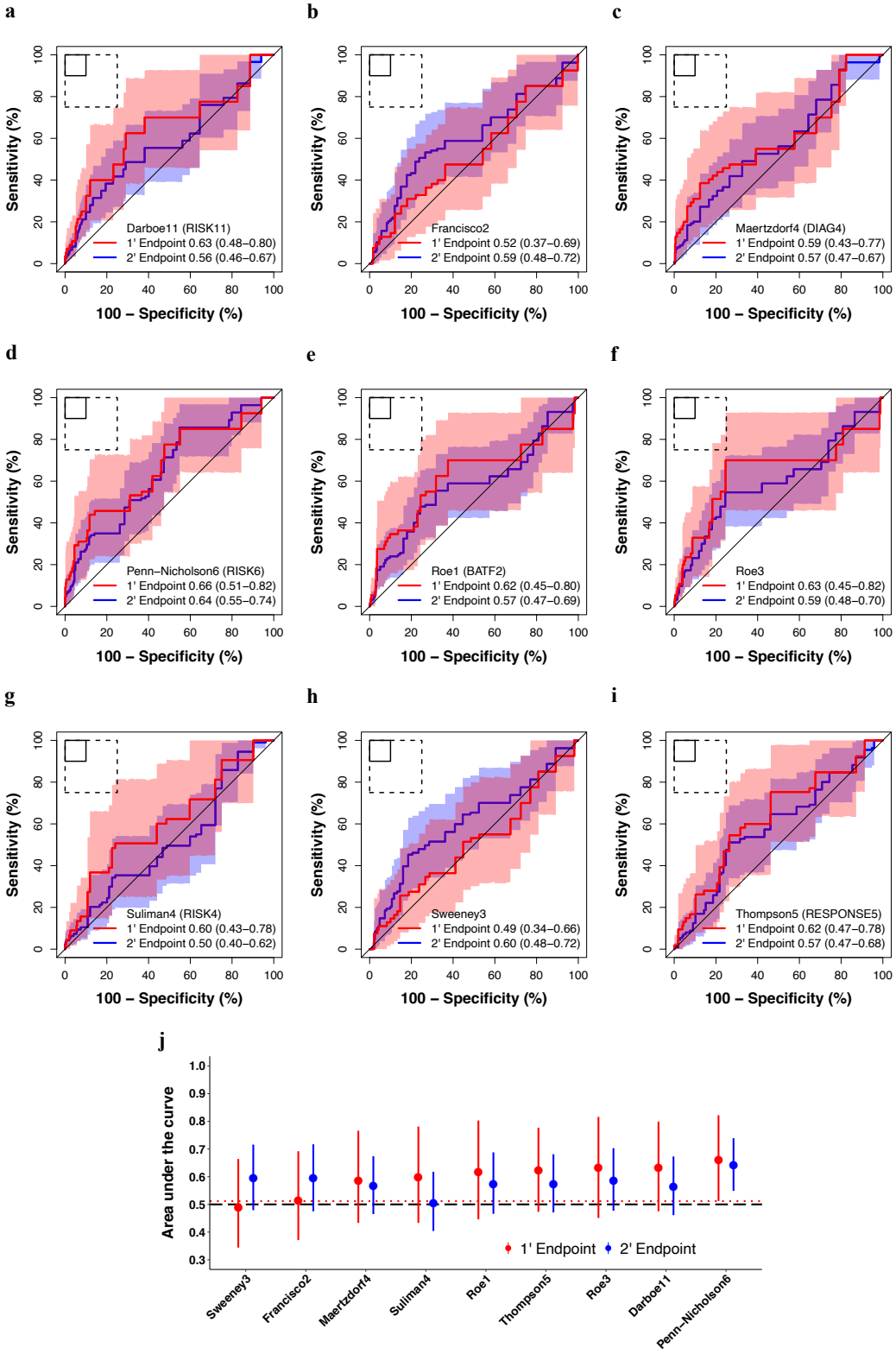

Figure S9: Parsimonious signatures prognostic performance for primary versus secondary endpoint TB through 15-months follow-up in people without HIV

Receiver operating characteristic (ROC) curves depicting primary ('1) versus secondary ('2) endpoint prognostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Penn-Nicholson6 (RISK6), (e) Roe1 (BATF2), (f) Roe3, (g) Suliman4 (RISK4), (h) Sweeney3, and (i) Thompson5 (RESPONSE5) signatures through 15-months follow-up in the CORTIS-01 study of people without HIV. The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (90% sensitivity and 90% specificity) and the dashed box depicts the minimal criteria (75% sensitivity and 75% specificity) set out in the WHO Target Product Profile for an incipient TB test.[4] (j) Summary of signature prognostic performance in order of primary endpoint AUC estimates. The prognostic AUC estimates for the secondary endpoint are also shown. The midline indicates the AUC estimate, the error bars indicate the 95% CIs, the red dotted line indicates the lower bound of the 95% CI for the best performing signature for the primary endpoint, and the black dashed line indicates an AUC cut-off of 0.5.

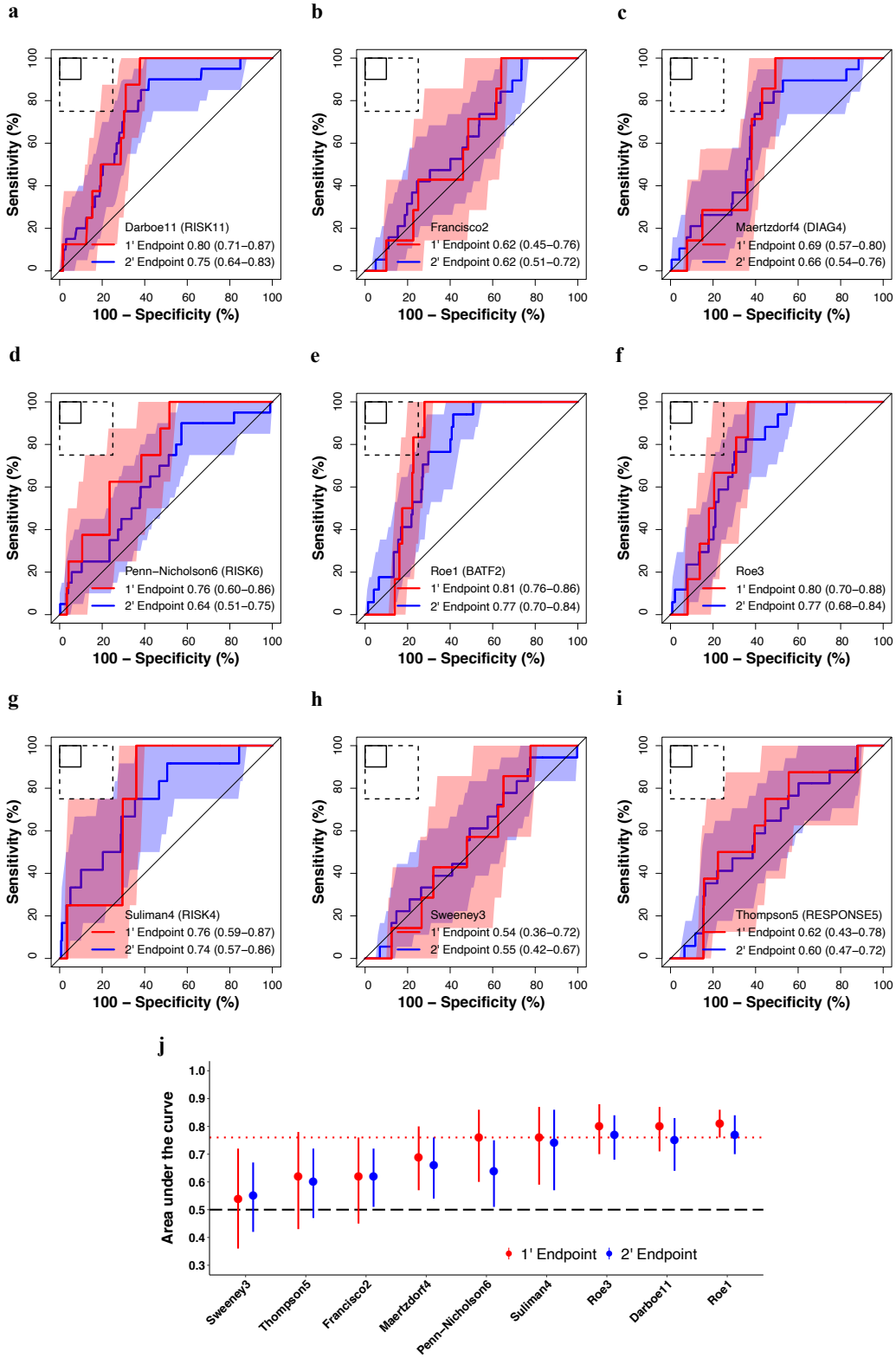

Figure S10: Parsimonious signatures prognostic performance for primary versus secondary endpoint TB through 15-months follow-up in people living with HIV

Receiver operating characteristic (ROC) curves depicting primary (‘1) versus secondary (‘2) endpoint prognostic performance (area under the curve, AUC, with 95% CI) of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Maertzdorf4 (DIAG4), (d) Penn-Nicholson6 (RISK6), (e) Roe1 (BATF2), (f) Roe3, (g) Suliman4 (RISK4), (h) Sweeney3, and (i) Thompson5 (RESPONSE5) signatures through 15-months follow-up in the CORTIS-HR study of people living with HIV. The shaded areas represent the 95% CIs. The solid box depicts the optimal criteria (90% sensitivity and 90% specificity) and the dashed box depicts the minimal criteria (75% sensitivity and 75% specificity) set out in the WHO Target Product Profile for an incipient TB test.[4] (j) Summary of signature prognostic performance in order of primary endpoint AUC estimates. The prognostic AUC estimates for the secondary endpoint are also shown. The midline indicates the AUC estimate, the error bars indicate the 95% CIs, the red dotted line indicates the lower bound of the 95% CI for the best performing signature for the primary endpoint, and the black dashed line indicates an AUC cut-off of 0.5.

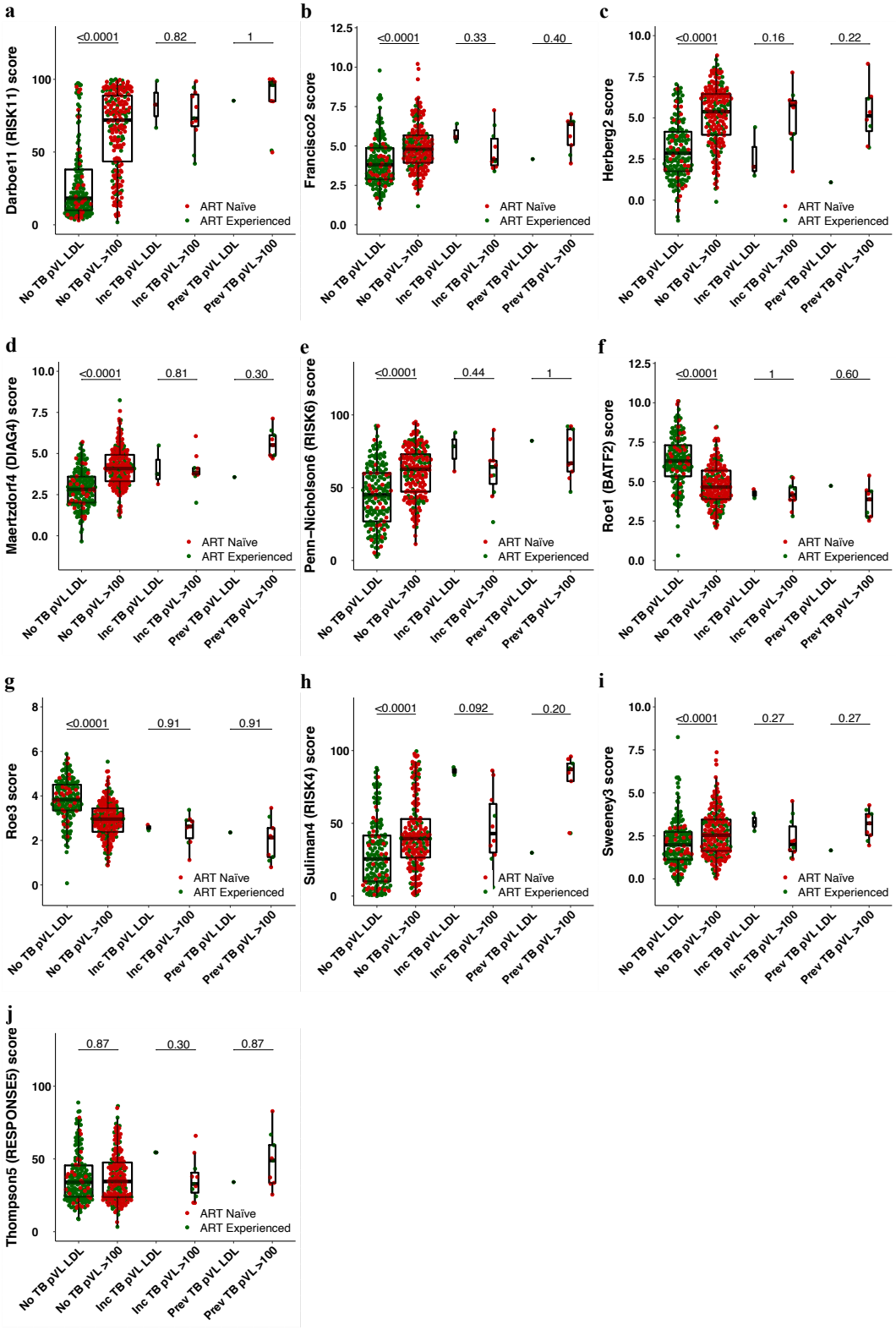

Figure S11: Parsimonious signatures score distribution by HIV plasma viral load

Box-and-whisker plots depicting distributions of the (a) Darboe11 (RISK11), (b) Francisco2, (c) Herberg2, (d) Maertzdorf4 (DIAG4), (e) Penn-Nicholson6 (RISK6), (f) Roe1 (BATF2), (g) Roe3, (h) Suliman4 (RISK4), (i) Sweeney3, and (j) Thompson5 (RESPONSE5) signature scores measured at baseline in the CORTIS-HR study stratified by HIV plasma viral load (copies per mL) and TB status. Prevalent (Prev) and incident (Inc) TB comprised all microbiologically confirmed secondary endpoint cases (i.e. TB confirmed on at least one sputum sample). HIV plasma viral load (pVL) is stratified into two groups: lower than the detectable limit (LDL) of 100 copies per mL and greater than 100 copies per mL (>100).
Each dot represents a participant. p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR).

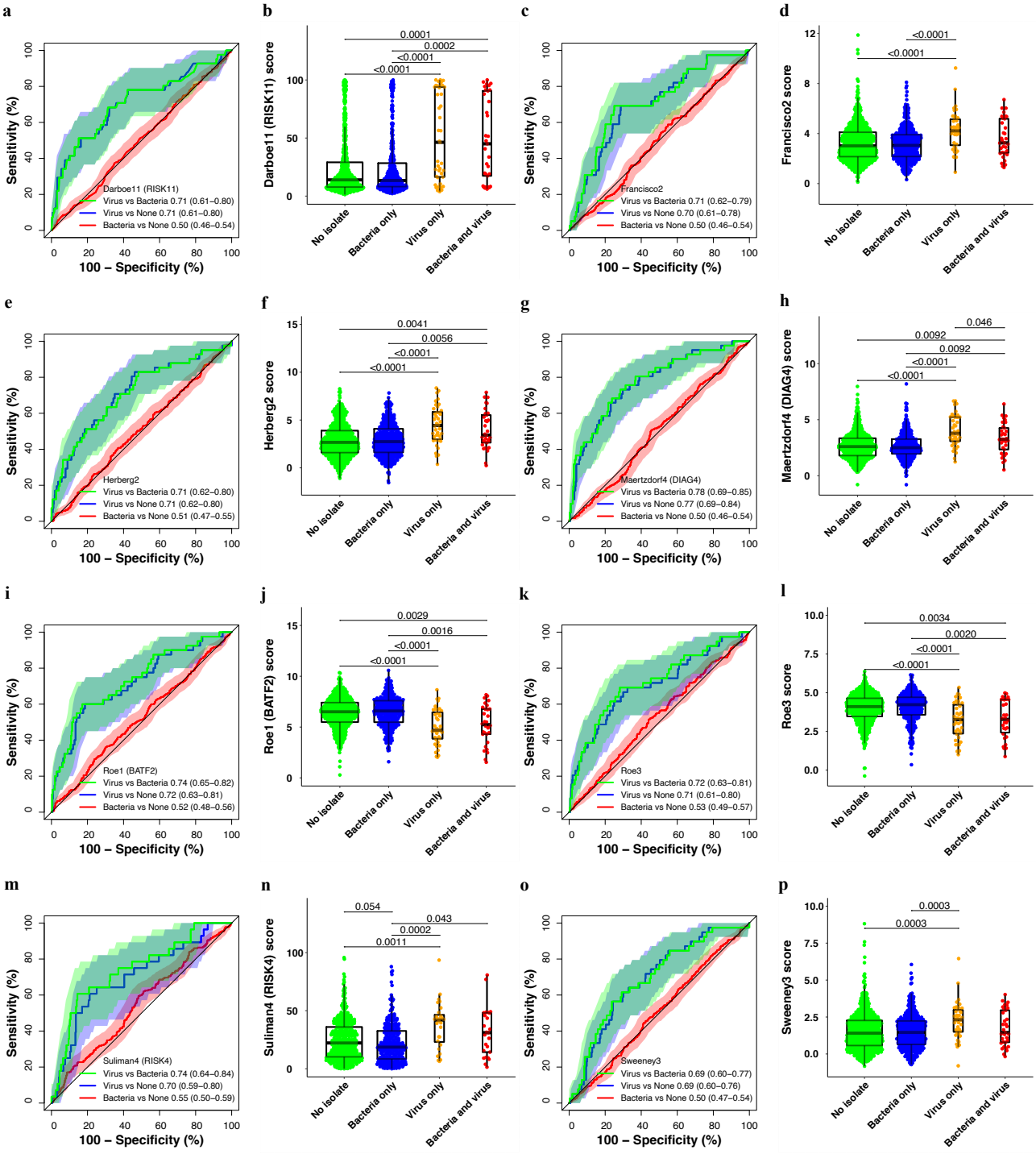

Figure S12: Parsimonious signature performance for differentiating participants with viral or bacterial upper respiratory tract pathobionts, and those without any pathobionts

Paired receiver operating characteristic (ROC) curves and box-and-whisker plots for the (a-b) Darboe11 (RISK11), (c-d) Francisco2, (e-f) Herberg2, (g-h) Maertzdorf4 (DIAG4), (i-j) Roe1 (BATF2), (k-l) Roe3, (m-n) Suliman4 (RISK4), and (o-p) Sweeney3 signatures in all participants without prevalent TB in the respiratory pathobionts sub-study (11 participants with secondary endpoint prevalent TB excluded). The box-and-whisker plots depict signature score distributions in participants with no upper respiratory pathobionts (n=563), bacterial upper respiratory pathobionts only (n=352), viral upper respiratory pathobionts only (n=41), both viral and bacterial upper respiratory pathobionts (n=33). p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Only p-values below 0.1 are shown. Each dot represents a participant. Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR). The ROC curves depict performance (area under the curve, AUC, with 95% CI) of the parsimonious signatures in differentiating between participants with viral upper respiratory pathobionts and participants with bacterial upper respiratory pathobionts, between participants with viral pathobionts and those with no pathobionts, or between participants with bacterial pathobionts and those with no pathobionts. The shaded areas represent the 95% CIs.

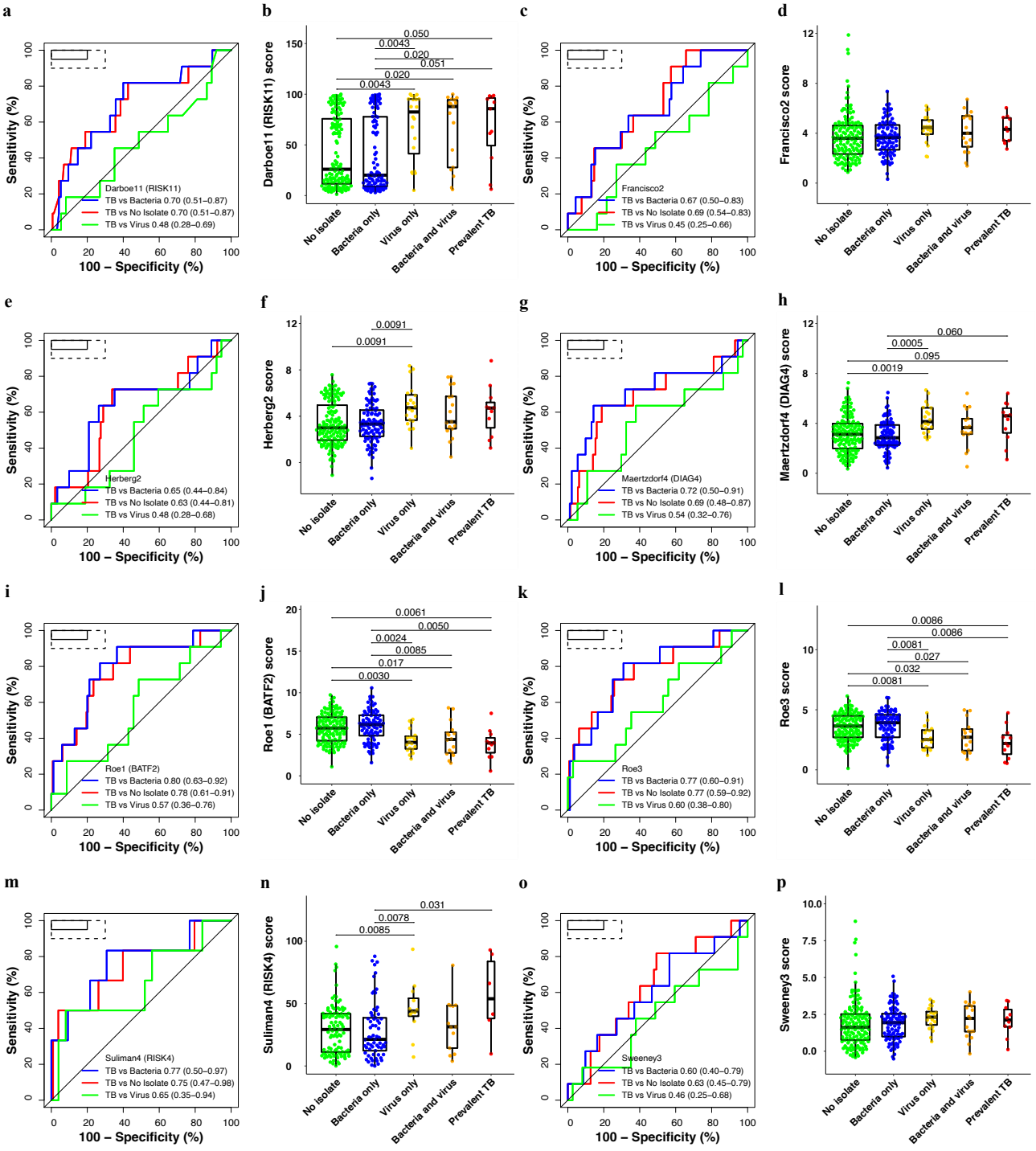

Figure S13: Parsimonious signatures performance for differentiating participants with TB from those viral or bacterial upper respiratory tract pathobionts, and those without any pathobionts

Paired receiver operating characteristic (ROC) curves and box-and-whisker plots for the (a-b) Darboe11 (RISK11), (c-d) Francisco2, (e-f) Herberg2, (g-h) Maertzdorf4 (DIAG4), (i-j) Roe1 (BATF2), (k-l) Roe3, (m-n) Suliman4 (RISK4), and (o-p) Sweeney3 signatures in all participants randomised in the CORTIS-01 study and co-enrolled in the respiratory pathobionts sub-study. Participants who were not randomised in the CORTIS-01 study, and thus not investigated for TB, are not included.

The box-and-whisker plots depict signature score distribution in participants with no upper respiratory pathobionts (n=143), bacterial upper respiratory pathobionts only (n=95), viral upper respiratory pathobionts only (n=20), both viral and bacterial upper respiratory pathobionts (n=17), and *Mycobacterium tuberculosis* (n=11) detected on GeneXpert MTB/RIF or MGIT culture (microbiologically-confirmed secondary endpoint prevalent TB; i.e. TB confirmed on at least one sputum sample). p values for comparison of median signature scores between groups in box-and-whisker plots were calculated with the Mann-Whitney *U* test and corrected for multiple comparisons by use of the Benjamini-Hochberg Procedure.[3] Only p-values below 0.1 are shown. Each dot represents a participant. Boxes depict the IQR, the midline represents the median, and the whiskers indicate the IQR ± (1.5 × IQR).

The ROC curves depict performance (area under the curve, AUC, with 95% CI) of the parsimonious signatures in differentiating between participants with prevalent TB (n=11) and participants with viral upper respiratory pathobionts (n=37), participants with bacterial upper respiratory pathobionts only (n=95), and participants with no pathobionts (n=143). Participants with both viral and bacterial pathobionts (n=17) were included in the group with viral pathobionts only (n=20) as the presence of bacterial pathobionts did not appear to affect signature scores.
The solid box depicts the optimal criteria (95% sensitivity and 80% specificity) and the dashed box depicts the minimal criteria (90% sensitivity and 70% specificity) set out in the WHO Target Product Profile for a triage test.[2]

Supplementary References

1. Penn-Nicholson A, Mbandi SK, Thompson E, Mendelsohn SC, Suliman S, Chegou NN, et al. RISK6, a 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response. Sci Rep. 2020;10(1):8629. doi: 10.1038/s41598-020-65043-8.
2. WHO. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. Geneva: World Health Organization, 2014. https://apps.who.int/iris/handle/10665/135617 (accessed May 22, 2020).
3. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal statistical society: series B (Methodological). 1995;57(1):289-300. doi: 10.1111/j.2517-6161.1995.tb02031.x.
4. WHO. Consensus Meeting Report: Development of a Target Product Profile (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection to active disease. Geneva: World Health Organization, 2017. http://apps.who.int/iris/handle/10665/259176 (accessed May 22, 2020).