National Institutes of Health
Turning Discovery Into Health

IMPERIAL

The discovery of monitoring biomarkers from the SHINE study

2024 IMPAACT Annual Meeting

Dr Claire Dunican

The “SHINE” trial - Shorter treatment for minimal tuberculosis (TB) in children

Aim: to assess the performance of shorter (4 months versus 6 months) TB treatment regime in children with smear-negative non-severe drug-susceptible TB disease.

Trial time-period: July 2016 - July 2018

Cohort: 1,204 children (2 months – 15 years, median: 3.5 years)

Location(s): Uganda, Zambia, South Africa and India.

Outcome: unfavourable status – by 72 weeks - “tuberculosis events (treatment failure, including treatment extension beyond the replacement of missed doses, antituberculosis-treatment drug change or restart due to suspected treatment failure, and tuberculosis recurrence as adjudicated by the end-point review committee), loss to follow-up during treatment, or death from any cause.”

Summary: children were randomly assigned to the 4 month or 6-month treatment groups (1:1) and the percentages of adverse outcomes compared between groups.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Authors: Anna Turkova, M.R.C.P.C.H., Genevieve H. Wills, M.Sc., Eric Wobudeya, M.Med., Chishala Chabala, M.Med., Megan Palmer, M.B., Ch.B., M.Med., Aarti Kinikar, M.D., Syed Hissar, M.D., M.P.H., +22, for the SHINE Trial Team* Author Info & Affiliations

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Abstract

BACKGROUND

Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.

METHODS

We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A

Conclusion: "Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, non-severe, smear-negative tuberculosis."

What's next….

….Use the blood samples from the trial participants to examine the performance of diagnostic and monitoring biomarkers over time

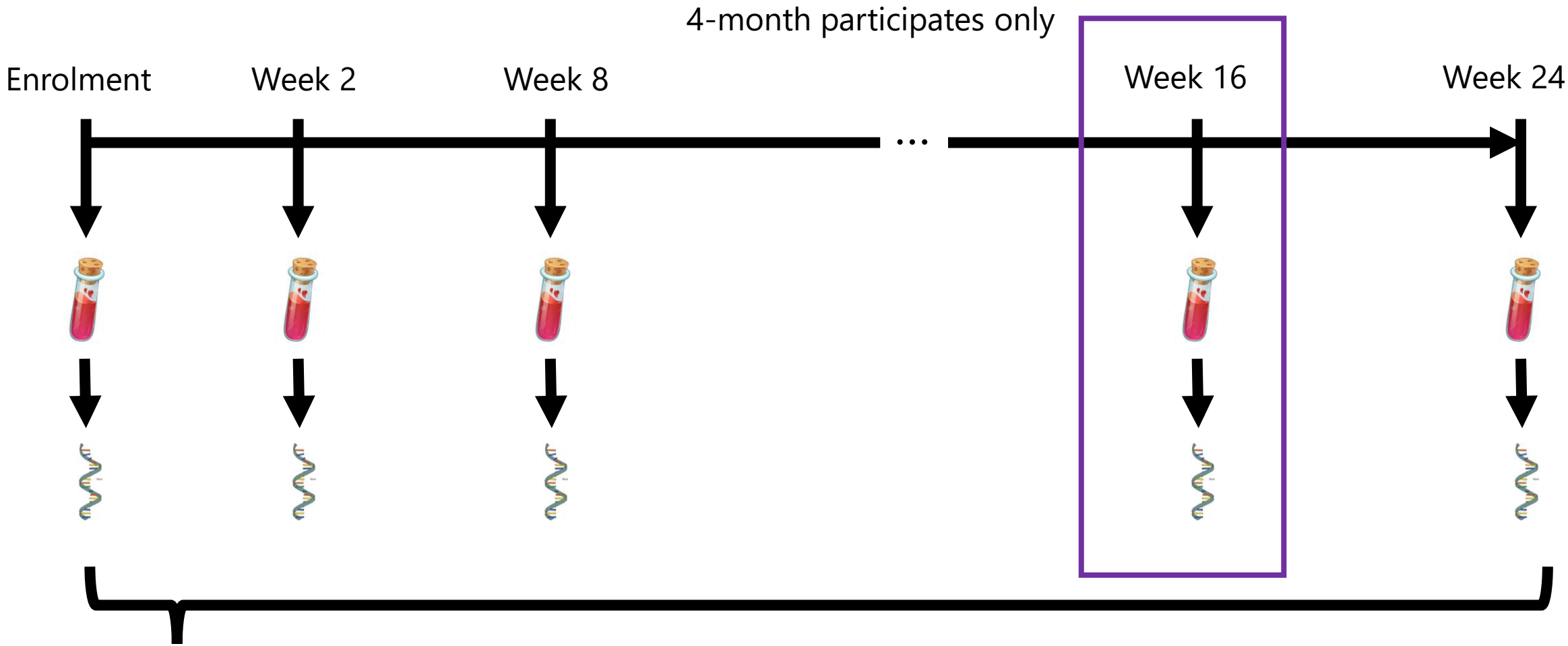
Biological question: do the two arms of the trial reach "normal" biomarker expression levels by their respective treatment end-points?

Solution: qPCR on known-TB associated genes

End of treatment

Enrolment Week 2 Week 8 … Week 16 Week 24

qPCR
n=809 (198 individuals)
Confirmed, Unconfirmed or Unlikely TB
85 genes pre-selected from the literature



qPCR
n=809 (198 individuals)
Confirmed, Unconfirmed or Unlikely TB
85 genes pre-selected from the literature

6-month participates only

Enrolment Week 2 Week 8 … Week 16 Week 24

qPCR
n=809 (198 individuals)
Confirmed, Unconfirmed or Unlikely TB
85 genes pre-selected from the literature

Aims

See Vanessa's talk!

1. ~~Examine the performance of existing signature scores over time (diagnostic, monitoring)~~
2. Discover new signatures on the dataset (diagnostic, monitoring)
3. Examine if performance differs significantly by trial arm
4. Examine the dynamics of the monitoring signature changes over time - to develop a score for changes in expression in response to treatment to assess if it can be ended early.

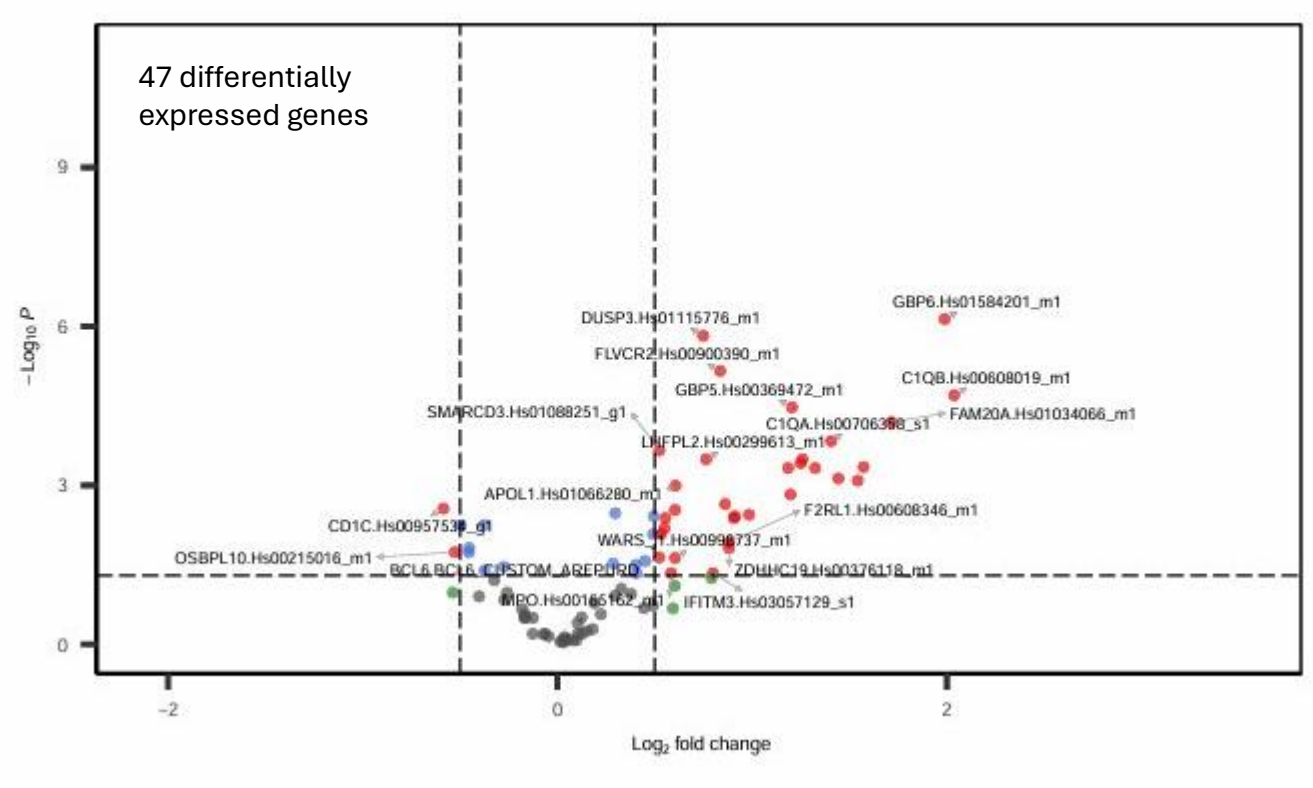
Aims:

Identify new biomarkers

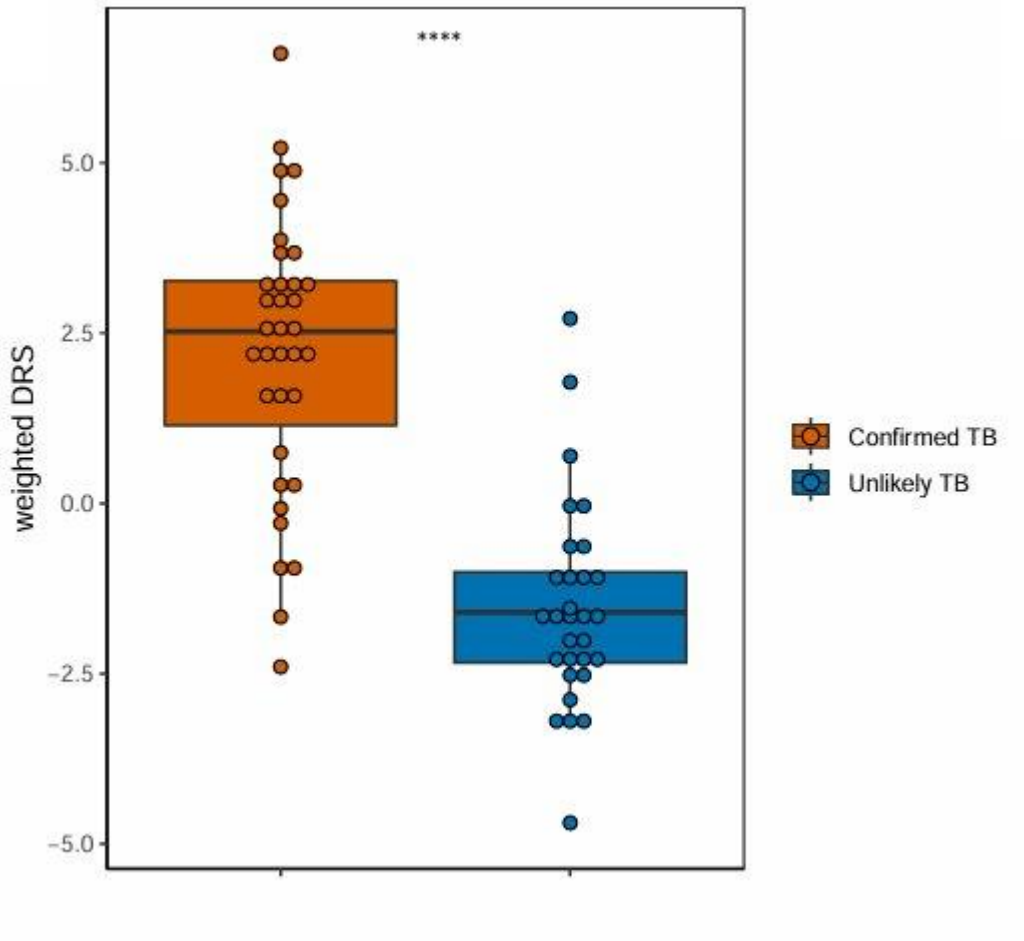
Determine if the performance significantly differs between trial arms

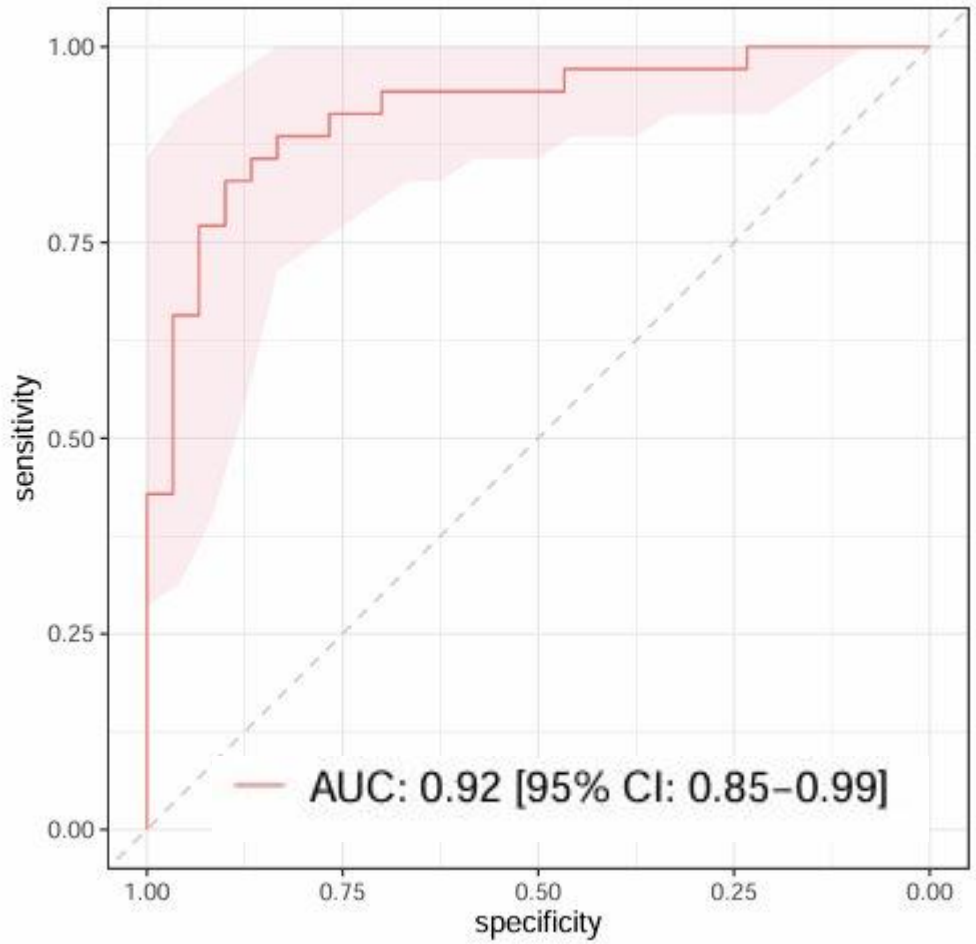
Diagnostic: confirmed vs unlikely TB (at enrolment)

Data Preprocessing → Differential expression analysis → Feature selection

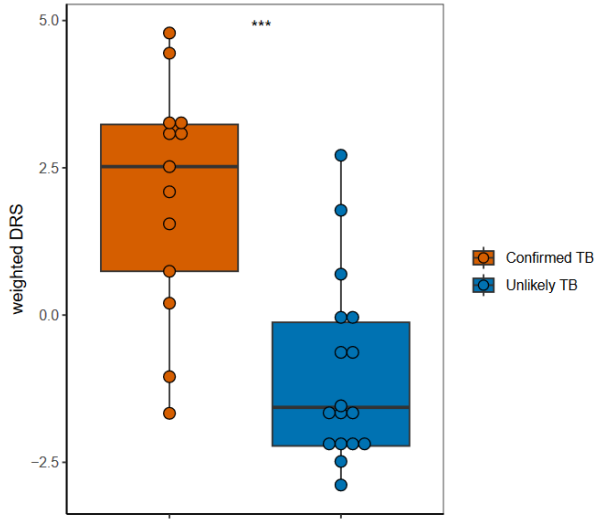


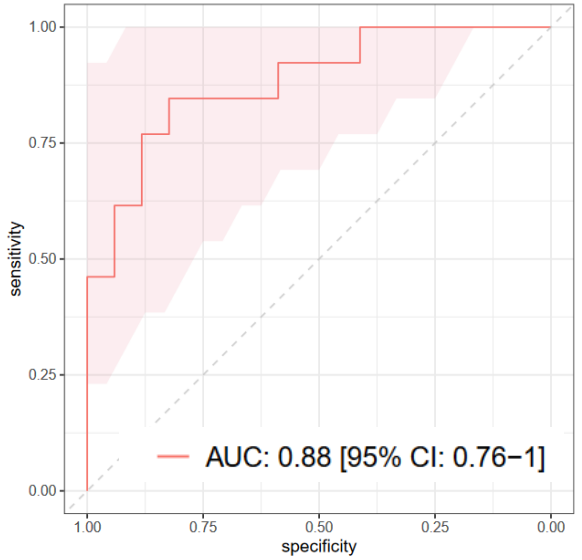
6 gene signature


****
weighted DRS
5.0
2.5
0.0
−2.5
−5.0
Confirmed TB
Unlikely TB

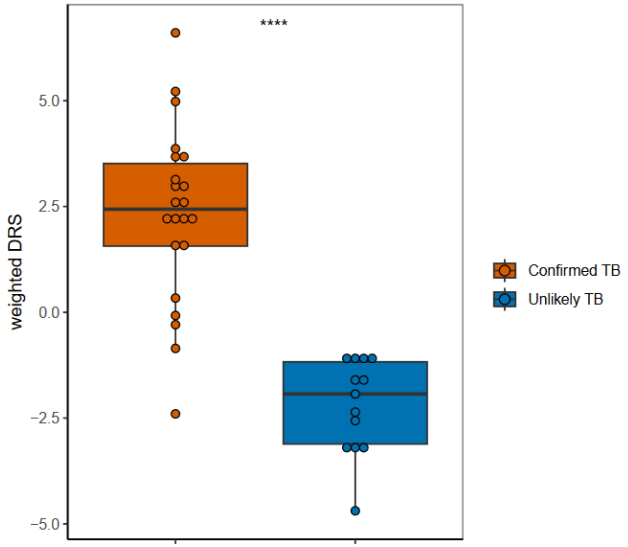

1.00
0.75
0.50
0.25
0.00
sensitivity
1.00
0.75
0.50
0.25
0.00
specificity
AUC: 0.92 [95% CI: 0.85–0.99]

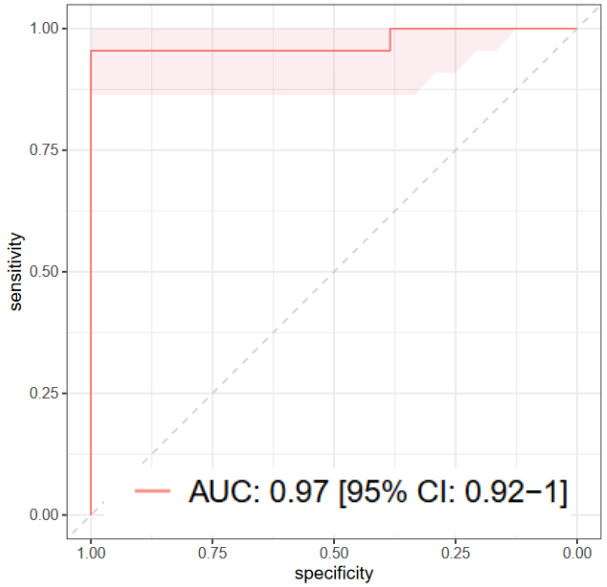
Arm 4





Arm 6

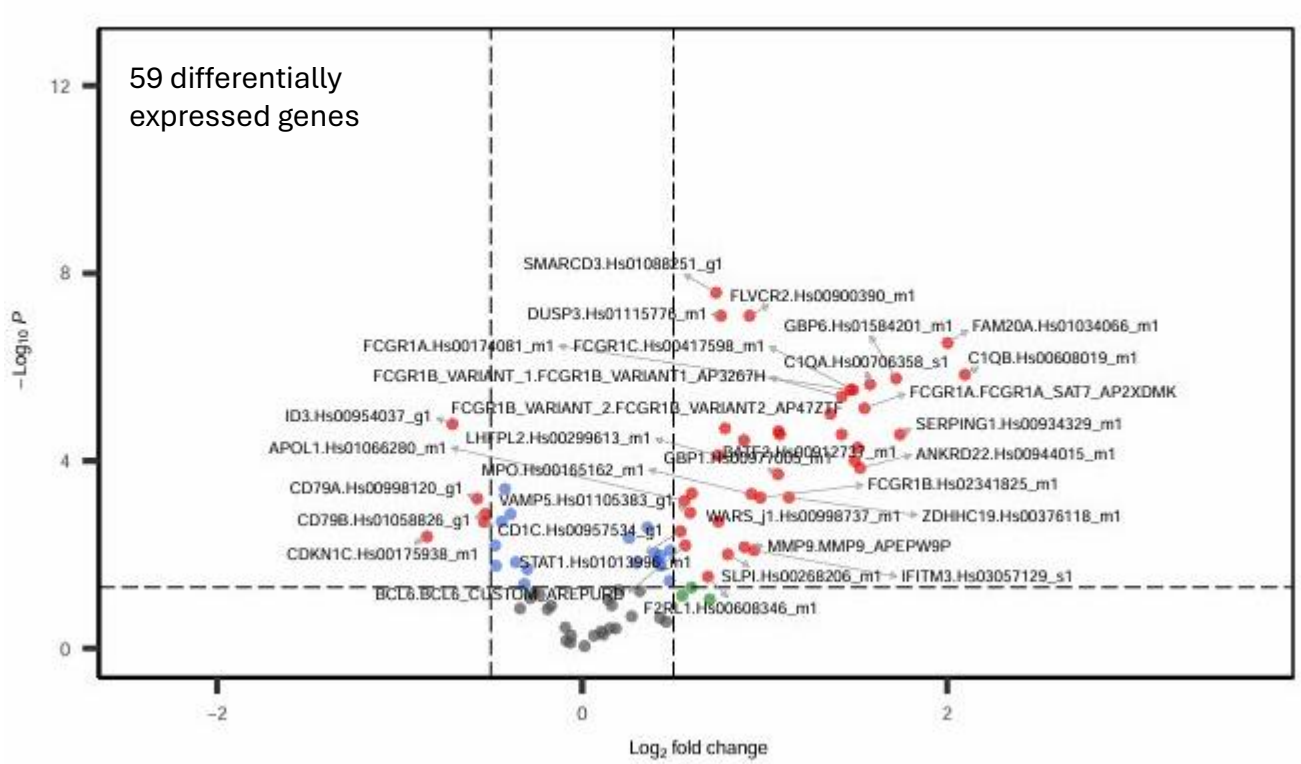




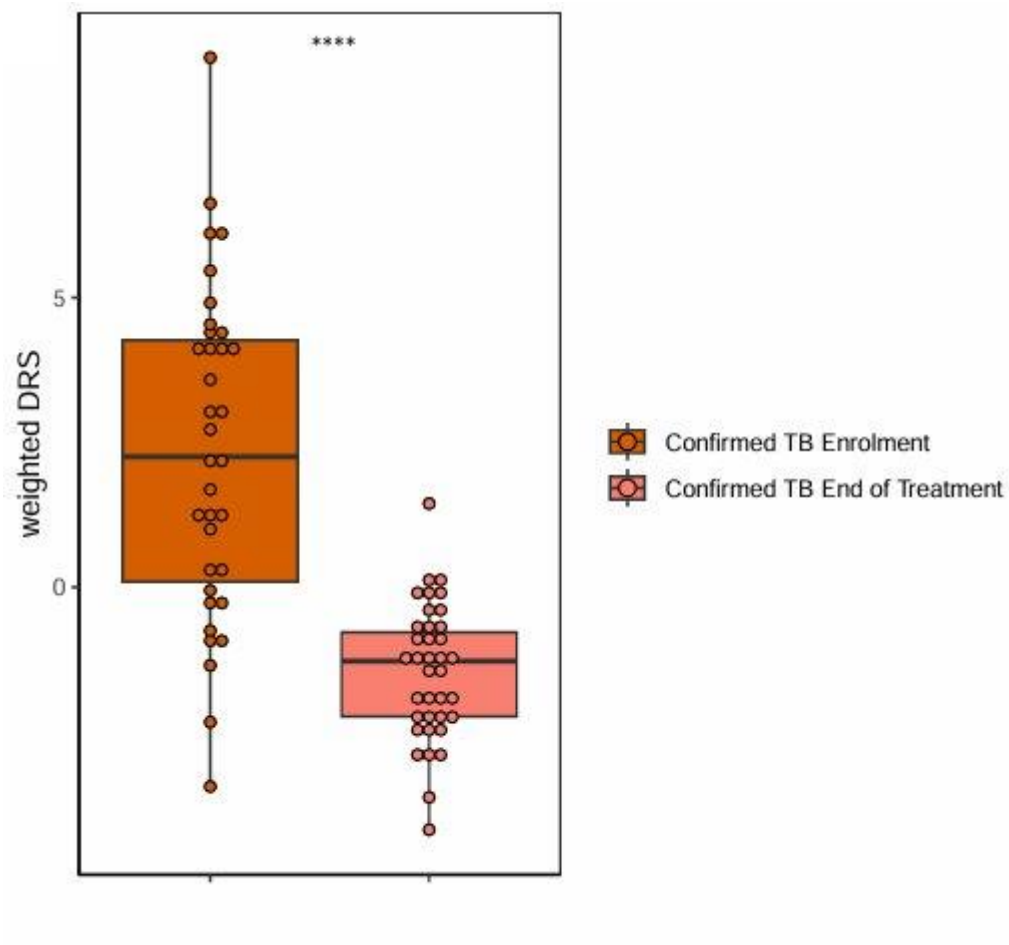
DeLong's test
p-value = 0.20

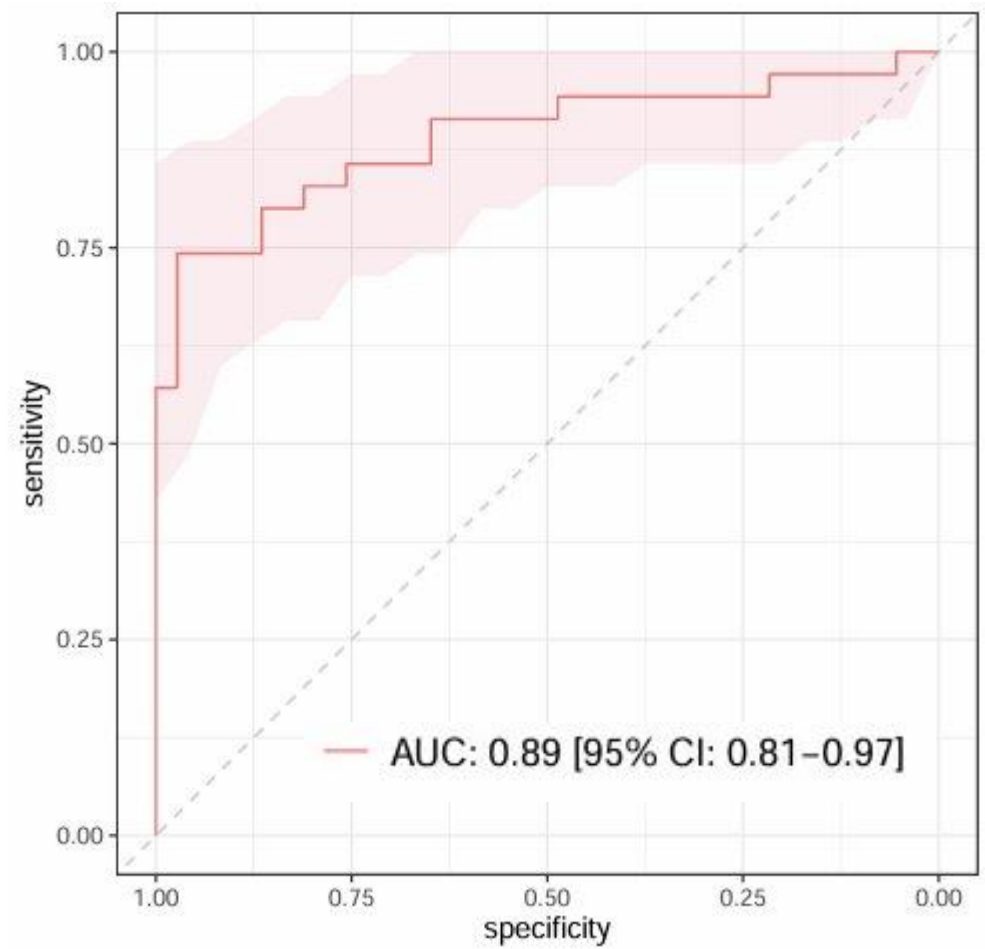
Monitoring: enrolment vs end of treatment (confirmed TB only)

Data Preprocessing → Differential expression analysis → Feature selection

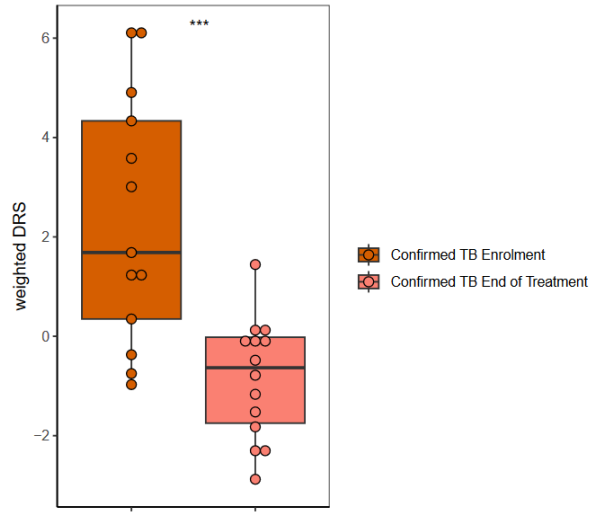


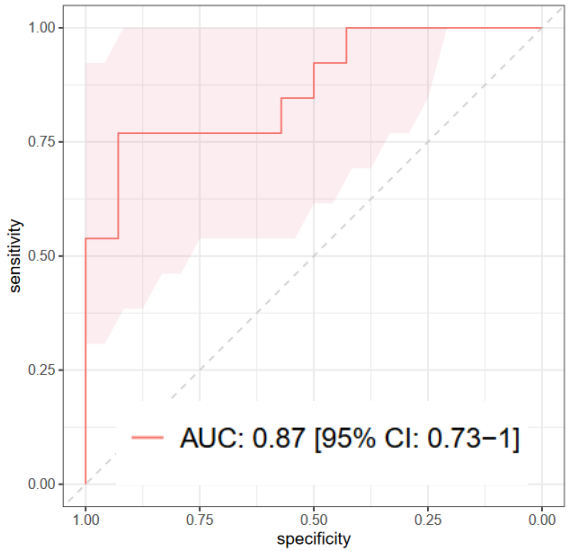
4 gene signature


****
weighted DRS
5
0
Confirmed TB Enrolment
Confirmed TB End of Treatment

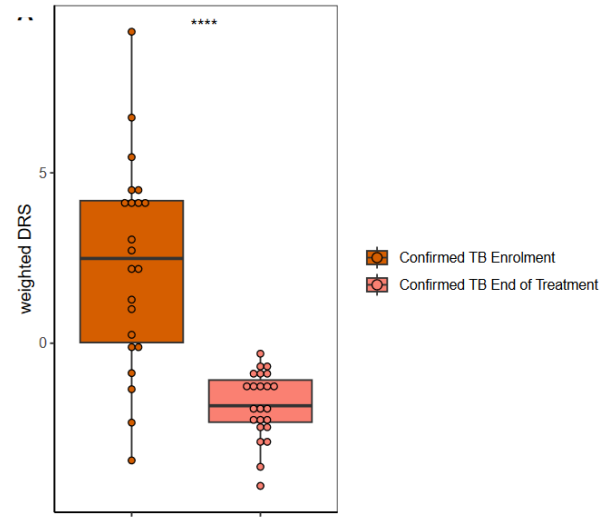

1.00
0.75
0.50
0.25
0.00
sensitivity
1.00
0.75
0.50
0.25
0.00
specificity
AUC: 0.89 [95% CI: 0.81–0.97]

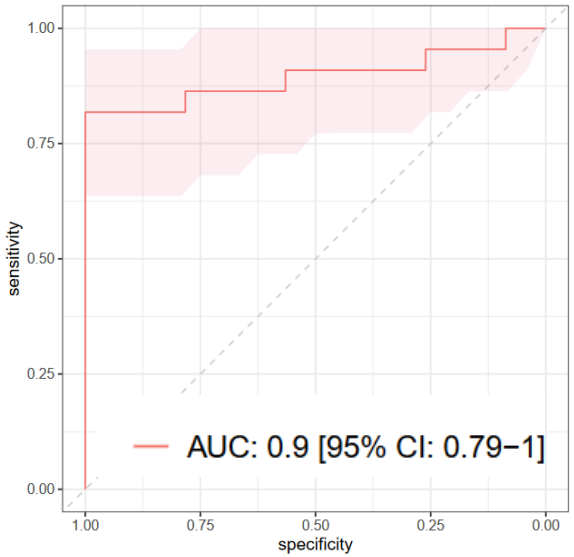
Arm 4





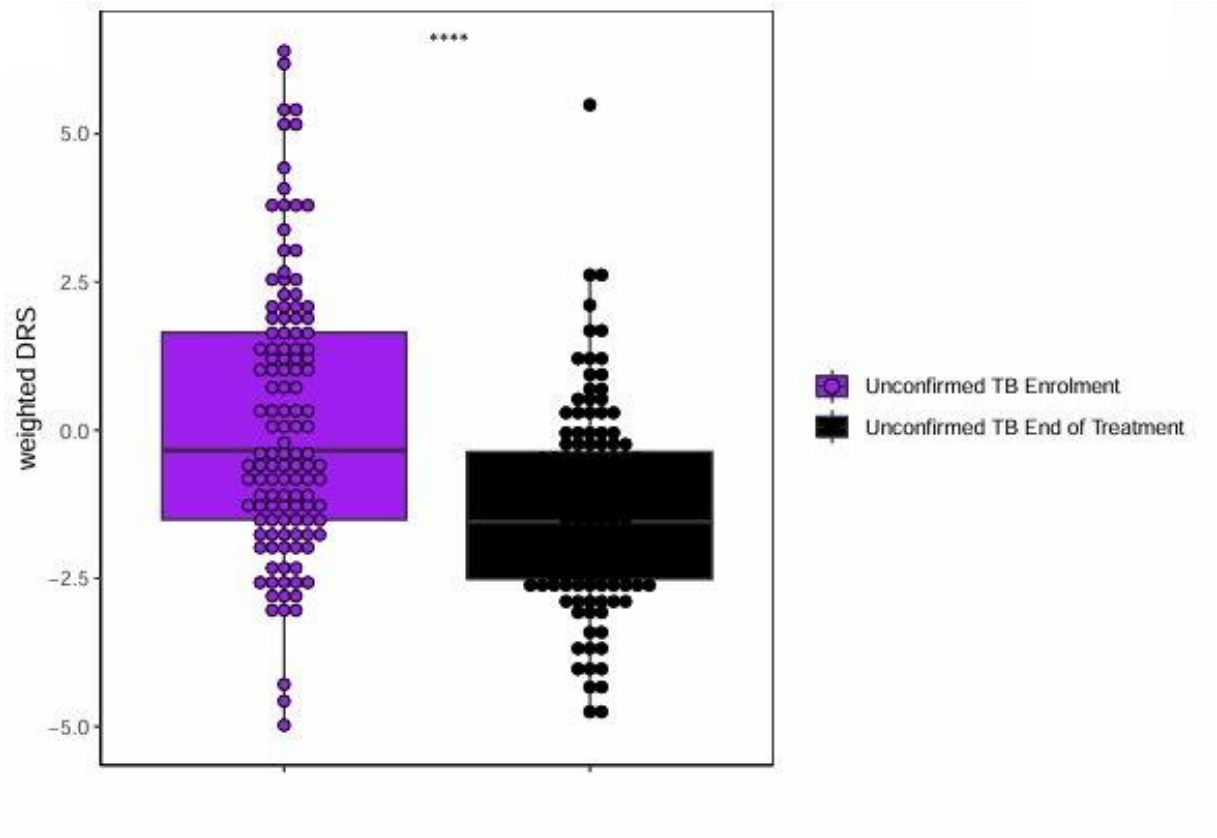
Arm 6

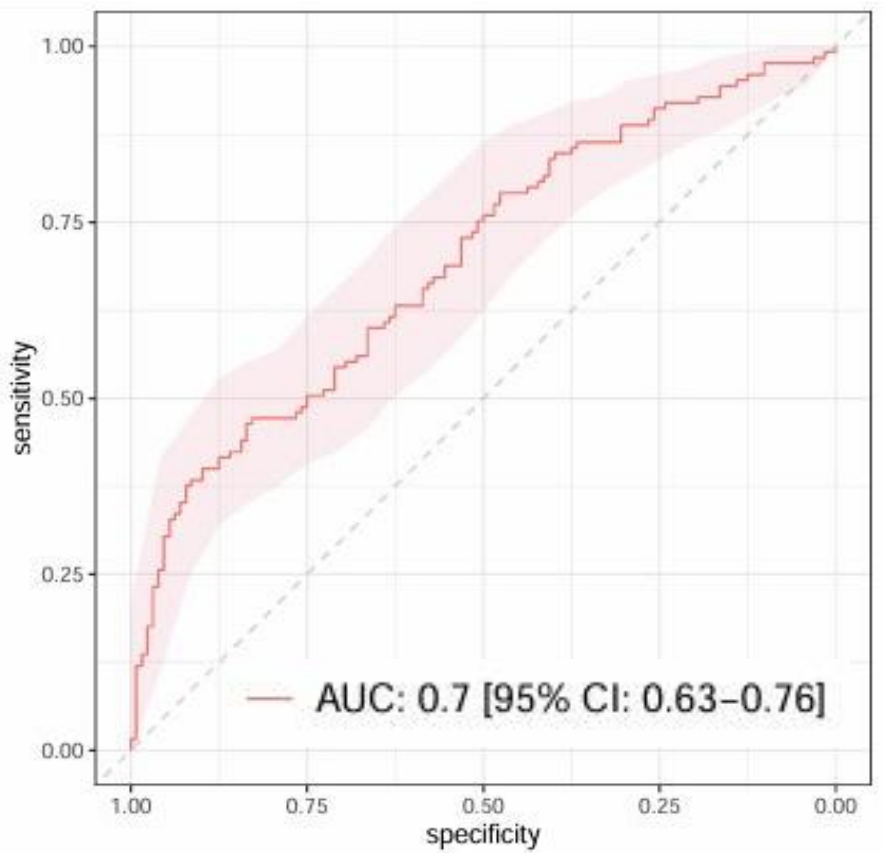




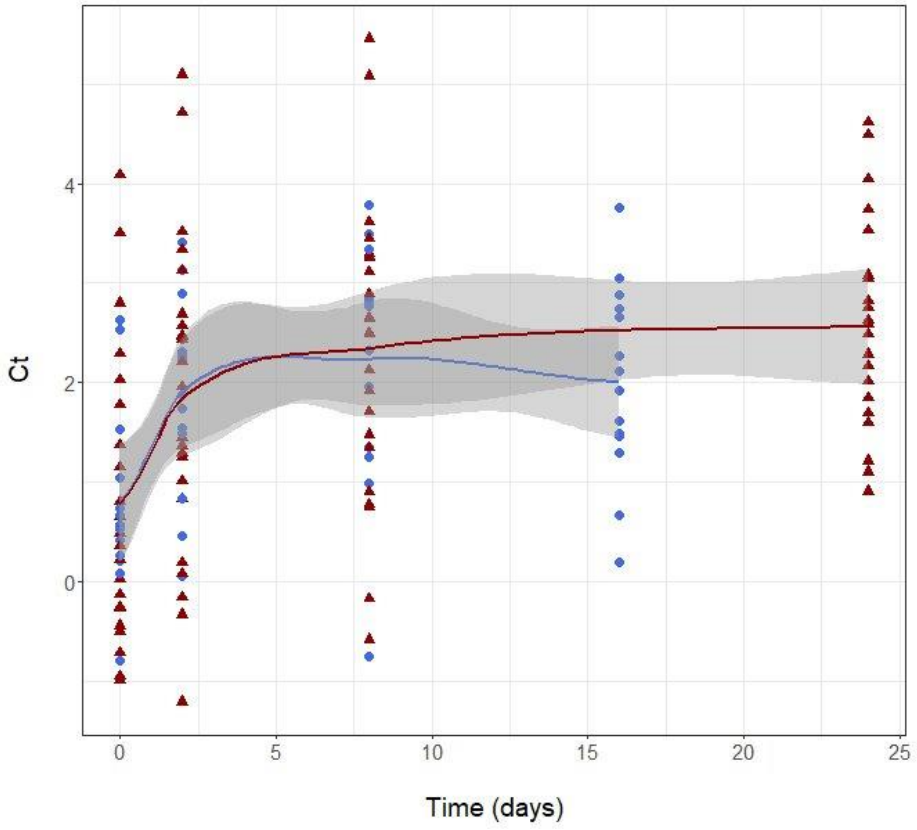
DeLong's test
p-value = 0.76

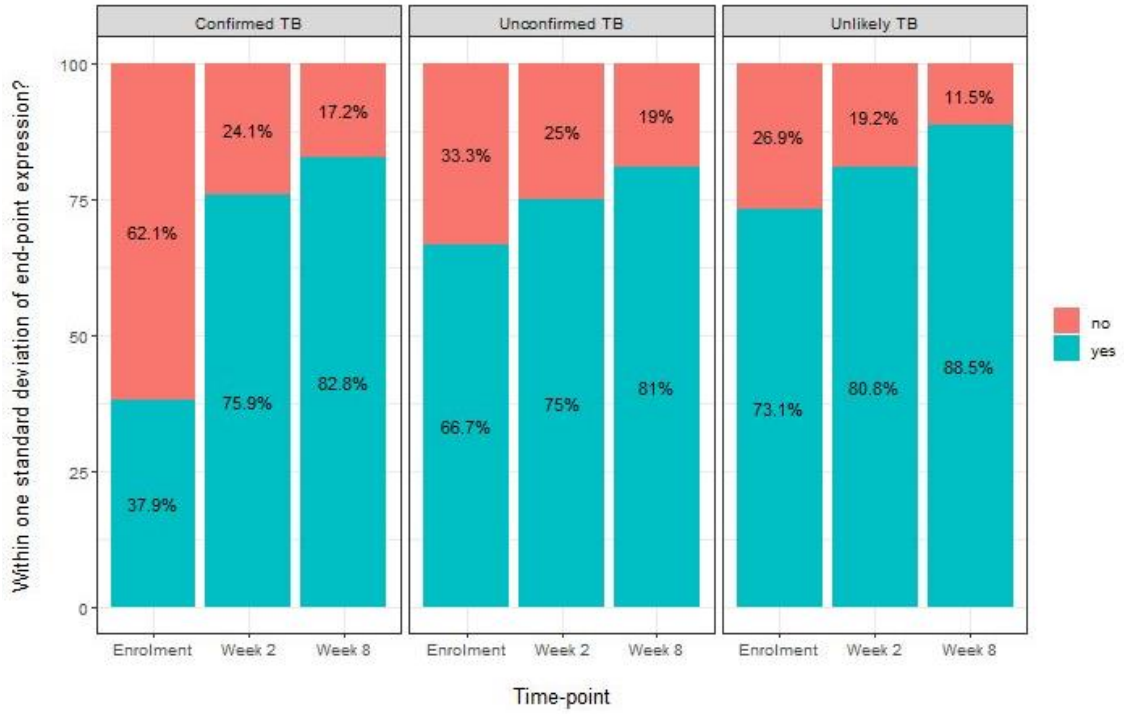
Performance in the unconfirmed-TB group:

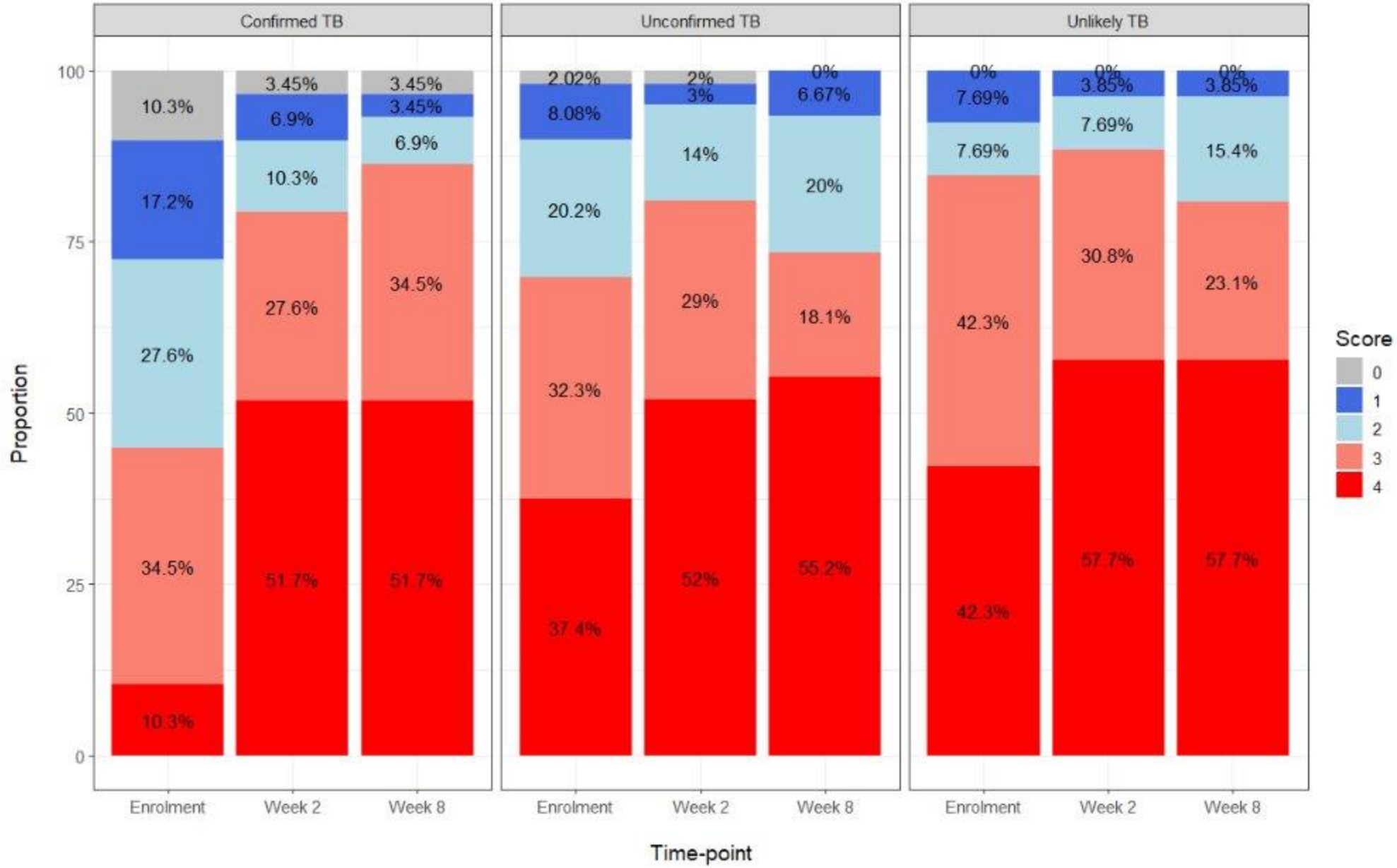


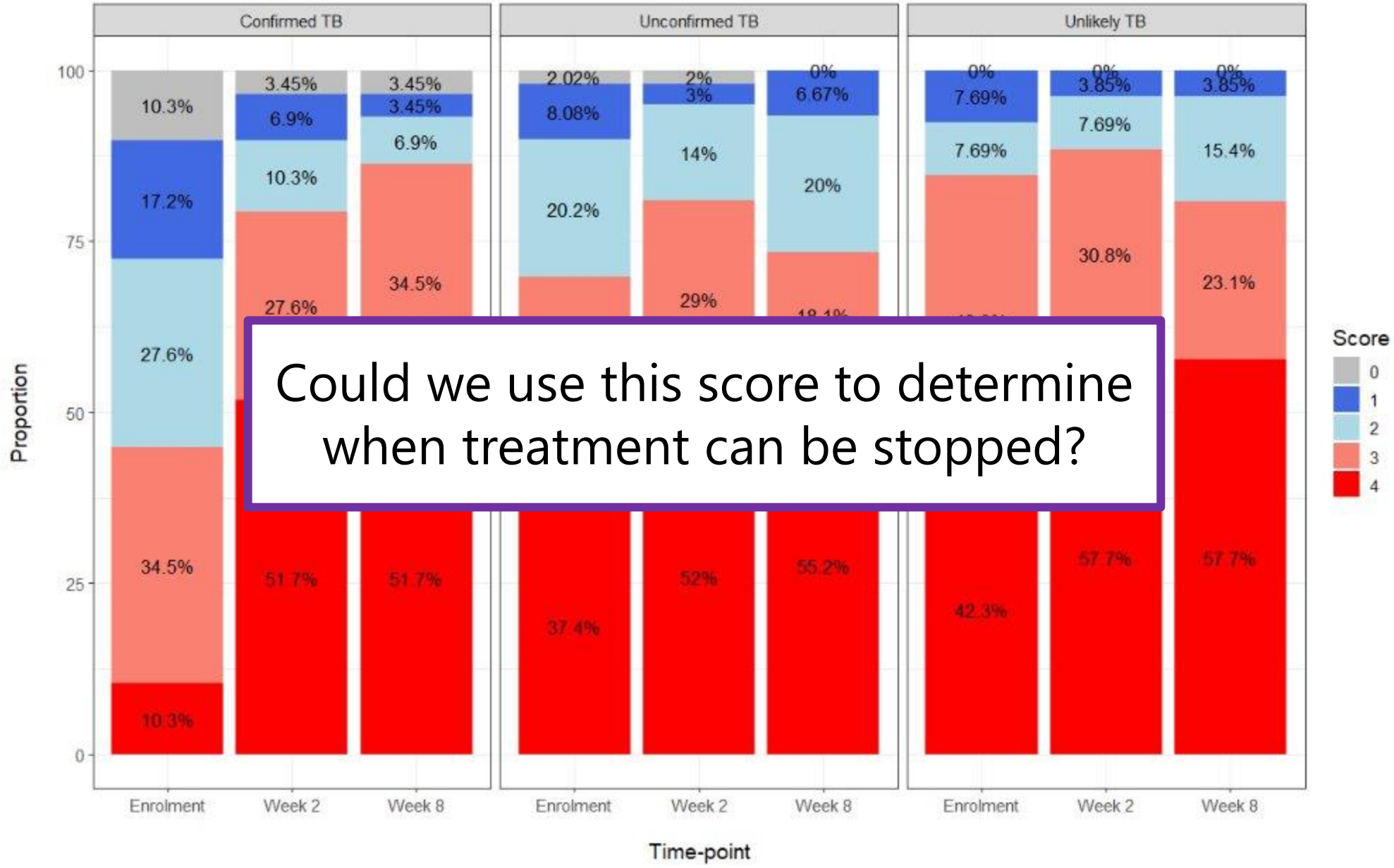


Aim: examine the gene expression dynamics over time to develop a score






Confirmed TB
Unconfirmed TB
Unlikely TB
Proportion
100
75
50
25
0
10.3%
17.2%
27.6%
34.5%
10.3%
3.45%
6.9%
10.3%
27.6%
51.7%
3.45%
3.45%
6.9%
34.5%
51.7%
2.02%
8.08%
20.2%
32.3%
37.4%
2%
3%
14%
29%
52%
0%
6.67%
20%
18.1%
55.2%
0%
7.69%
7.69%
42.3%
42.3%
0%
3.85%
7.69%
30.8%
57.7%
0%
3.85%
15.4%
23.1%
57.7%
Enrolment
Week 2
Week 8
Time-point
Score
0
1
2
3
4



Could we use this score to determine when treatment can be stopped?

Summary

Using the qPCR data from the TB-SHINE trial we have:

- Identified small diagnostic and monitoring biomarker signatures
- Demonstrated how the performance of these biomarkers does not significantly differ between trial arms.
- Demonstrated proof of principal of how these signatures can be used to develop a monitoring score that could be used to help determine when treatment can be stopped.

Future work – biomarker validation in an external cohort!

Acknowledgements

South Africa Team: [1]Muwanga VM, [1]Mendelsohn SC, [1]Mbandi SK, [1]Erasmus M, [1]Raphela R, [1]Hadley K, [1]Bilek N, [2]Van der Zalm MM, [2,3]Demers A [2]Palmer M [2]Hesseling AC, [4]Gibb D, [4]Turkova A, [2,5]Seddon JA*, [1]Scriba TJ*, and the SHINE Trial consortium

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