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Blood-based tuberculosis precision medicine: transcriptomic model predicts treatment response

Keywords: tuberculosis (TB), MDR-TB, XDR-TB, transcriptomic analysis, whole blood, culture conversion, therapy monitoring, treatment response

INVENTION NOVELTY

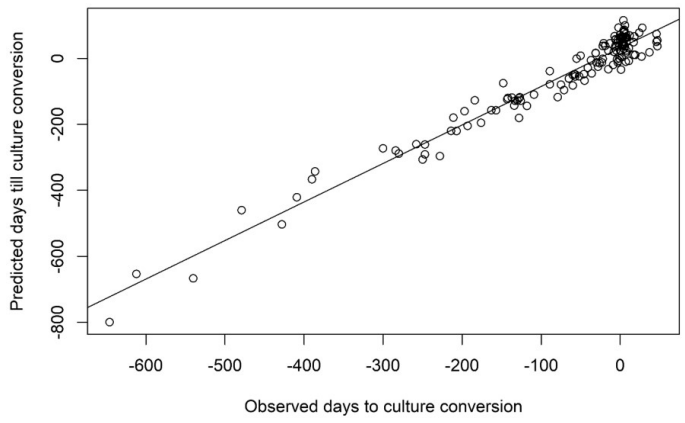
Tuberculosis (TB) remains a major global health problem, aggravated by the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (Mtb). Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are associated with high treatment costs, severe side effects, and poor outcomes. Current guidelines recommend a standardized treatment duration (>12 months for MDR-/XDR-TB), but individual treatment success and duration vary widely depending on factors such as immune status, drug-resistance, and drugs used. Treatment monitoring typically involves cultivating patient samples to determine bacterial growth, with so-called culture conversion indicating the moment when the patient is no longer contagious. However, although this cultivation method is very sensitive, it suffers from at least two major limitations, i.e., patient samples (e.g., sputum) are not always available, and Mtb grows extremely slow, requiring several weeks to obtain reliable data. The innovation provides a transcriptomic model for precision medicine that accurately calculates the time to culture conversion from a simple blood sample within hours at any single time-point of Mtb infection and anti-TB therapy, overcoming the limitations of the cultivation method.

VALUE PROPOSITION

The transcriptomic model represents a versatile and valuable tool for blood-based TB precision medicine. It enables reliable prediction of therapy response and the clinically important time to culture conversion for both drug-sensitive (DS-) and MDR/ XDR-TB. The model uses patient's whole blood and enables accurate forecast from any given time-point of infection and therapy. Apart from treatment monitoring, the model also represents a valuable tool for the development and evaluation of novel TB drugs.

TECHNOLOGY DESCRIPTION

206 patients with DS- (n=74) und MDR/XDR-TB (n=132) were recruited. Study visits occurred at defined time-points before the initiation of treatment, after culture conversion, and after the end of therapy, and included a clinical assessment as well as the collection of whole-blood for RNA measurements employing gene expression microarrays. Raw data were extracted, normalized, and subjected to quality control before building and training a transcriptomic model to predict the time to culture conversion. The model employs a three-step procedure and a total of 29 expression markers. Using the training dataset, the model accurately predicted the days to culture conversion with a correlation factor (r) of 0.98. Importantly, the model assigns patients with co-morbidities in a clinically plausible manner. For instance, immuno-compromised patients take longer to reach culture conversion, which is accurately reflected in the model's predictions.



Model validation in test data set. *Predicted vs. observed days till culture conversion. (Reimann et al., unpublished).*

DEVELOPMENT STATUS

Data of patients were divided into an identification cohort (n=149) and validation cohort (n=57). For model development, the identification cohort was again divided into a training and a test set (70:30). The former was used for the training of the transcriptomic model, whereas the latter was used for validation. In all cases, the correlation factor for calculating the time to culture conversion was ≥0.97 and the average difference between observed and calculated time was 1.7 days with an interquartile range of -4.9 to 11.6 days. Further clinical validation is in progress, but in principle the model is ready for use.

COMMERCIAL OPPORTUNITY

The model is available for co-development and in-licensing.

PATENT SITUATION

Priority-establishing EP patent application EP23175551.3 has been filed in May 2023.

FURTHER READING

Reimann *et al*. (2023) manuscript in preparation.

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