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HOST–PATHOGEN INTERACTIONS IN TUBERCULOSIS: A MULTI-OMICS AND ARTIFICIAL INTELLIGENCE PERSPECTIVE

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Abstract

Although much progress has been made on the detection, treatment, and prevention of TB, it remains one of the most lethal infectious diseases globally. M. tuberculosis remains a complex pathogen with highly variable host–pathogen interactions, which have contributed to its persistence over time. These interactions influence susceptibility, immune response, disease course, and treatment outcome, and can vary widely between individuals.

While traditional studies have provided useful mechanistic insights, studying individual genes, proteins, or pathways may not be sufficient to understand the complex and heterogeneous disease process. New multi-omics platforms facilitate the study of various biological systems in parallel. Genomics, epigenomics, transcriptomics, proteomics, and metabolomics have all undergone tremendous advances recently, and further advances in single-cell and spatial multi-omics are expected to reveal new dimensions of pathogen biology, host immune response, cellular heterogeneity, and TB-specific signatures.

However, interpreting these large and heterogeneous datasets requires specialized tools that allow the extraction of biologically relevant and clinically actionable knowledge from the data. AI and machine learning have emerged as powerful tools for multi-omics data integration, biomarker discovery, risk stratification, and individualized diagnostic and therapeutic applications.

Recent progress in host–pathogen interactions, multi-omics, and AI offer unprecedented opportunities to develop precise approaches for TB control. There remain, however, several obstacles to address before these advances can be effectively translated to clinical practice. These include the challenge of understanding the underlying biology, inadequate sample sizes and cohort representativeness, methodological inconsistencies, difficulties in data integration and model interpretability, and unequal availability of technological infrastructure.

In this review, we explore the potential of multi-omics and AI to better understand the pathophysiology of TB and its host–pathogen interactions, and support biomarker discovery, risk prediction, and patient-specific disease management. We further consider the main scientific, technical, and implementation barriers that need to be overcome to advance towards clinical application.

Frontier in Medical & Health Research

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1. Introduction

1.1 Tuberculosis as a Global Health Challenge

Tuberculosis (TB) caused by Mycobacterium tuberculosis (M. tuberculosis) continues to be a major global public health problem. Although the disease predominantly affects the lungs, it can occur in other organs as well, resulting in a wide variety of clinical presentations (Chakaya et al., 2021). Despite availability of effective antimicrobial therapy and the Bacillus Calmette–Guérin (BCG) vaccine, TB control remains a significant public health concern due to continued transmission, prolonged treatment, and socioeconomic and health disparities (Gilmour & Alene, 2024). The increasing prevalence of multidrug-resistant and rifampicin-resistant TB further complicates the management of TB by limiting the available treatment options and increasing the cost and length of therapy (Farhat et al., 2024).

TB infection is heterogeneous in its presentation. It is not a binary state (latent or active), but rather a spectrum that ranges from asymptomatic latent infection controlled by immunity to active disease that develops when immune control is lost (Migliori et al., 2021). The degree of infection depends on numerous variables including host susceptibility, immune status, and bacterial factors. Therefore, identifying individuals at risk of progression to disease and predicting treatment outcomes is a major challenge (Zaidi et al., 2023). Further elucidating the molecular and immunologic mechanisms underlying host susceptibility, adaptation of M. tuberculosis, and disease progression may help in developing novel tools to prevent, diagnose, and treat TB (Zhuang et al., 2024).

1.2 Why Host–Pathogen Interactions Matter

The outcome of a TB infection depends on the interaction between the pathogenic bacterium Mycobacterium tuberculosis and the host immune response (Mohammadnabi et al., 2024).

Following infection of the host by M. tuberculosis, the microbe is exposed to a variety of host cells, including macrophages, dendritic cells, and various other innate immune cells (Chandra et al., 2022). M. tuberculosis has developed mechanisms to avoid intracellular killing, modulate host signaling, and survive in the host. Moreover, host-specific factors like genetics, immune profile, metabolism, and the local tissue microenvironment play important roles in susceptibility and resistance (Park et al., 2024).

Thus, the outcome depends on the balance between protective immunity and pathology: If the host response is too weak, the bacterium can proliferate and cause progressive disease, but if it is too strong or dysregulated, inflammation can result in further tissue destruction and worse clinical consequences (Jarczak & Nierhaus, 2022). This interplay is fundamental to understanding how a person will present clinically. Even though two people might get infected with the same organism, they may experience different diseases because of underlying molecular and immunological differences (Casanova & Abel, 2022).

Understanding these differences may help predict the clinical outcome and identify new biomarkers and therapeutic targets. Also, understanding the host pathways that either protect against or promote disease may offer new approaches to host-directed therapy (Gholap et al., 2025). Lastly, understanding the host factors required to prevent disease due to M. tuberculosis infection may help to design better vaccines and more robust correlates of protection (Gholap et al., 2025).

1.3 From Reductionist Biology to Systems-Level TB Research

While many studies investigating TB to date have targeted individual genes, proteins, cytokines, or signaling pathways, such reductionist approaches do not sufficiently address the complexity of this multifactorial disease, which involves numerous factors including host genetics, immunity, bacteria, metabolism, and environment (Alipoor et al., 2026). Thus, few if any molecular markers or pathways have been sufficient to explain the large spectrum of biological and clinical diversity observed in TB (Kwok et al., 2021).

Recent advances in high-throughput ‘omics’ have provided an opportunity to shift focus from a singular approach to a systems-level approach to the study of TB. Genomics, transcriptomics,

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proteomics, metabolomics, and epigenomics each provide insights into complementary aspects of host and pathogen biology that together help us understand the molecular underpinnings of infection and disease (Shafqat Rasool, 2026). The addition of single-cell and spatial technologies allows this view to be refined further by providing insight into heterogeneity within cellular subpopulations and capturing the spatial relationships of cells in complex tissue structures like the TB granuloma (Pyle et al., 2025).

However, it remains challenging to integrate information across different layers of biology. Artificial intelligence (AI) and machine learning have emerged as tools that can help identify meaningful signals, integrate multi-modal data, and build predictive models from these massive datasets (Xu et al., 2024).

1.4 Scope and Objectives of the Review

In this review, we summarize the role of multi-omics and artificial intelligence in the current comprehension of M. tuberculosis-host interactions and their contribution to the advent of precision tuberculosis.

By bringing together the current understanding of host immunity, pathogen adaptation, molecular heterogeneity, and systems biology, we show how each of these components contributes to a better characterization of TB. Furthermore, we describe how genomics, transcriptomics, proteomics, metabolomics, and emerging single-cell and spatial techniques have been used to identify molecular signatures and biomarkers of TB with potential clinical applications.

We also discuss the possible applications of artificial intelligence as an overarching analytical tool that can aid existing approaches in combining different types of data, identifying significant biological relationships and developing models that can be applied to the prediction, diagnosis and treatment of TB.

Lastly, we consider some of the challenges that need to be addressed before multi-omics and machine learning can successfully transition from bench to bedside, including issues relating to sample variability, analytical methods, clinical validation, model transparency, cost, and global availability of advanced technologies.

Ultimately, we use this review to bridge the gap between M. tuberculosis and host biology on one hand and multi-omics and computational methodologies on the other hand in order to describe how traditional TB research is moving toward precision tuberculosis and to highlight some of the possible barriers to the translation of this paradigm shift into clinical practice.

2. Host–Pathogen Interactions in Tuberculosis

Tuberculosis (TB) arises from the complex interaction between M. tuberculosis and host immunity. TB is a dynamic process that results from both bacterial survival and proliferation as well as activation of innate and adaptive host immune responses (Chandra et al., 2022).

Depending on the outcome of these opposing processes, the infection may resolve, be contained, progress to active disease, or spread to other organs.

2.1 Establishment of Infection and Granuloma Formation

Transmission of M. tuberculosis usually occurs via inhalation of airborne droplets containing M. tuberculosis into the lungs (Sarkar & Sarkar, 2025). In the lungs, the bacilli are taken up by alveolar macrophages, the first cells in the host immune system to respond. Within these cells, macrophages attempt to kill the bacilli with several different mechanisms. Some of the M. tuberculosis survive inside macrophages, where they replicate or persist (Mai et al., 2024).

The innate immune response results in the release of proinflammatory molecules (such as cytokines and chemokines) that recruit additional immune cells to the site of infection (Qiu et al., 2012). Eventually, a mixture of cells, including infected macrophages, lymphocytes, and others, assemble to form granulomas, a feature associated with TB pathogenesis. Granulomas appear to be protective in limiting the dissemination of M. tuberculosis but also permit the persistence of long-term infection, suggesting that the granuloma response is not necessarily advantageous for the host (Elkington et al., 2022).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

2.2 Innate Immune Responses

Innate immunity serves as the first line of defense against infection with M. tuberculosis. In addition, innate immunity contributes to the outcome of early infection (Sankar & Mishra, 2023). Macrophages are key players because they serve as the primary host cell and the primary source of antimicrobial factors. Limiting infection requires several functions of macrophages, including phagocytosis, antimicrobial factor production, autophagy, antigen presentation, and cytokine secretion (Chen et al., 2023). Other cells of the innate immune system also contribute to the antimicrobial response. Dendritic cells link the innate and adaptive immune responses by processing and presenting antigen to T cells. Neutrophils are rapidly recruited to the site of infection and may contribute to the antimicrobial response, although neutrophil recruitment can also promote inflammation and tissue damage. NK cells contribute to the early immune response by producing cytokines and interacting with infected cells (Margraf et al., 2022).

Therefore, the effectiveness of innate immunity depends not only on the strength of the response but also its regulation. A controlled response leads to decreased bacterial replication and the initiation of adaptive immunity, whereas unregulated inflammation causes tissue damage and facilitates disease progression (Vu et al., 2024).

2.3 Adaptive Immune Responses

While the innate immune response plays an important role in the initial phase of infection, the adaptive immune response is key for long-term control of M. tuberculosis. $CD4^+$ T cells are an essential part of the adaptive immune response since these cells coordinate cell-mediated immunity through secretion of cytokines, which activate macrophage antimicrobial functions such as IFN-\u03b3 and TNF-\u03b1 ("CD4 Helper T Cells & CD4 T Cells Function + Isolation," ; Chatzileontiadou et al., 2020). CD8+ T cells are involved in protection via cytotoxicity and the secretion of other cytokines. However, it is thought that the extent of CD8+ T cell involvement is probably dependent on the type and length of the disease process. The role of B cells and humoral immunity has also been reevaluated in recent years due to their potential contribution in antigen presentation, cytokine secretion, and antibody production ("CD8+ T cell metabolism in infection and cancer | Nature Reviews Immunology,").

Crucially, the adaptive immune response must be tightly regulated; while regulatory T cells may serve to modulate and attenuate excessive inflammation and prevent pathological tissue damage, over inhibition of the adaptive response could result in failure to control M. tuberculosis. It is, therefore, not only the quantity of the adaptive immune response but also its quality and site of action, which determine successful host defense against M. tuberculosis (Okeke & Uzonna, 2019).

2.4 Immune Evasion and Host Manipulation

M. tuberculosis' ability to manipulate multiple cellular defense mechanisms likely contributes to its ability to survive within the host. One such mechanism includes interfering with phagosome maturation, limiting the fusion of phagosomes with lysosomes and decreasing intracellular killing. In addition, M. tuberculosis is known to inhibit autophagy and impair other cellular pathways involved in controlling intracellular pathogens (Cui et al., 2019).

Infection is accompanied by global shifts in the metabolic profile of infected cells including shifts in macrophage metabolism, nutrient supply and lipid metabolism. These changes have been shown to impact intracellular survival (Willmann & Moita, 2024). In addition, M. tuberculosis is known to influence host cytokine levels and intracellular signaling which may affect both pro-inflammatory responses and immunosuppressive signal(Diao et al., 2026).

M. tuberculosis' ability to manipulate multiple cellular defense mechanisms likely contributes to its ability to survive within the host. Importantly, it appears as if these pathways work in a concerted manner rather than in isolation. Intracellular trafficking, metabolism, inflammation and immunosuppression are all altered during infection suggesting that the ability to target one pathway in isolation may be of limited utility for

Frontier in Medical & Health Research

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understanding the pathogenesis of TB infection (Ghoshal et al., 2024).

Instead, the development of methods capable of evaluating the host response on a global scale during infection is critical for the advancement of our understanding of host-pathogen interactions in the context of TB infection (Nasiri & Venketaraman, 2025).

2.5 Host Genetic and Molecular Determinants of Susceptibility

Similarly, the clinical outcome of M. tuberculosis exposure can differ widely between people, suggesting that susceptibility is determined by both pathogen features and host factors. Host genetic differences may affect pathogen recognition, antigen presentation, cytokine signaling, and immune efficacy (Muraduzzaman et al., 2022). For instance, variation in human leukocyte antigen (HLA) genes might impact antigen presentation and T-cell recognition, while polymorphisms in Toll-like receptor (TLR) genes might impact early detection of pathogens and innate immune activation (Ruiz-Pablos et al., 2025). Variation affecting cytokine-associated pathways may influence inflammatory responses and disease progression.

Nevertheless, it is unlikely that the variation in TB susceptibility can be accounted for by single gene variants (Ismail et al., 2021). The outcome of the disease is probably governed by a combination of host genetics, immune profiles, environmental factors and characteristics of the pathogen itself (Kyabaggu et al., 2026).

There is a similar complexity at the molecular level. Transcriptional profiling studies have provided gene expression signatures associated with active disease, latent infection, disease progression and response to treatment, providing further evidence that these molecular data represent more than just a surrogate for population-level risk (Ismail et al., 2021). Thus, host genetics and molecular responses contribute to the diverse clinical outcomes of M. tuberculosis exposure, laying the groundwork for a systems-level investigation of TB using genomic, transcriptomic and other omics-based approaches (Ahamad et al., 2022).

Volume 4, Issue 3, 2026

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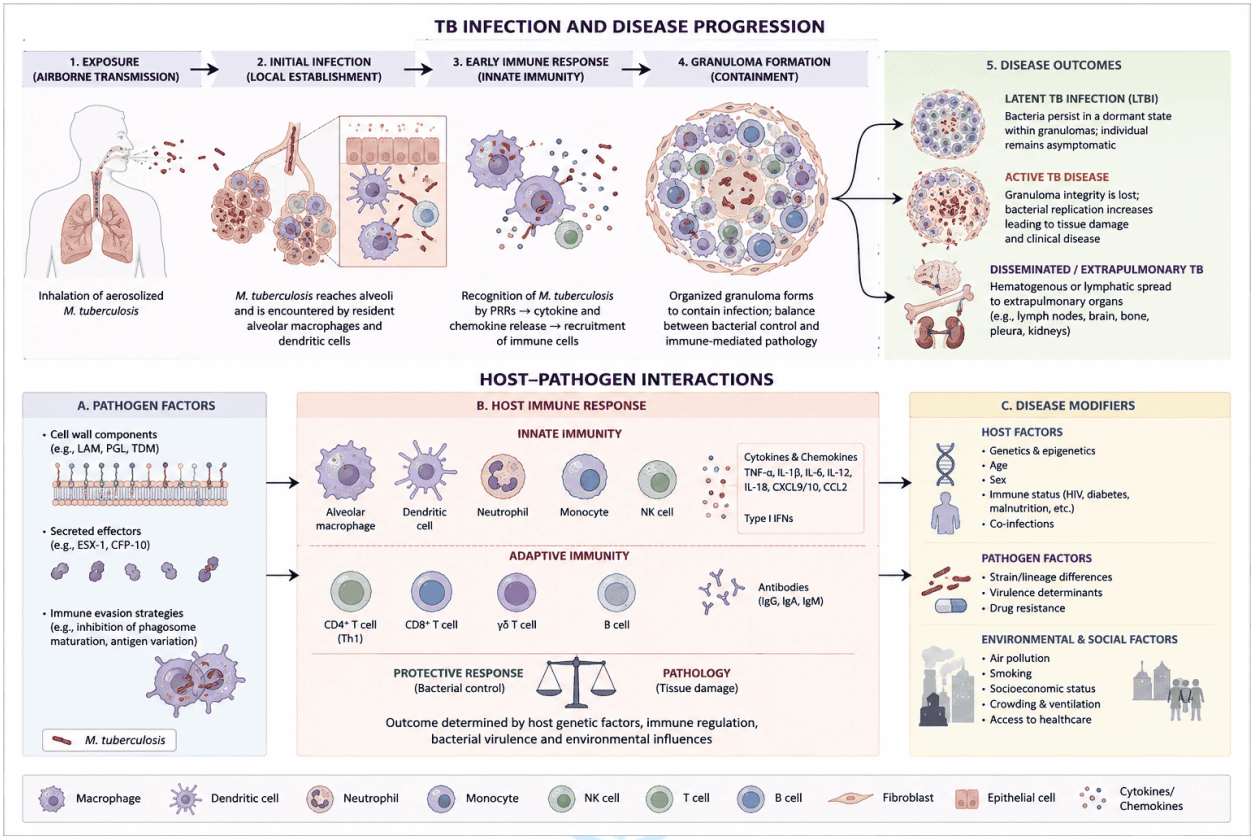

Figure 1. Integrated overview of host–pathogen interactions during tuberculosis infection and disease progression.

Upon inhalation of aerosolized M. tuberculosis, bacilli arrive in the lung alveoli, where they encounter innate immune cells (e.g., alveolar macrophages and dendritic cells). Early detection of the pathogen elicits an innate and then an adaptive immune response, which drives recruitment and accumulation of immune cells to form granulomas. The extent of protective immunity versus pathology affects whether the bacteria are cleared or persist, how much tissue injury occurs, and the severity of clinical disease. Furthermore, the outcome is determined by properties of the pathogen and host genetics and immunology, as well as social and environmental risk factors, resulting in latent TB infection, active TB disease, or TB disease with dissemination.

3. Multi-Omics Technologies for Deciphering Tuberculosis

Tuberculosis is a complex disease that cannot be attributed to the action of just one type of molecule. Rather, it is the product of the interaction between the genetics of M. tuberculosis, host genetic background, immune response, metabolism, and tissue microenvironment (Allué-Guardia et al., 2021).

A combination of several types of omics—or multi-omics—is a promising approach for investigating this multifaceted question. Omics, which encompasses genomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiome analysis, allows us to characterize DNA, RNA, proteins, metabolites, lipids, and microbes, respectively (Dai & Shen, 2022; Shafqat Rasool, 2026).

By integrating information derived from multiple omics, we can gain a more holistic understanding

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

of TB, as opposed to limiting our view to that of a single omics modality, and move away from viewing the disease solely in molecular terms toward focusing on the host-pathogen interaction (Vinhaes et al., 2024).

3.1 Genomics and Epigenomics

The use of genomic methods has improved our knowledge of M. tuberculosis diversity and host factors that contribute to susceptibility to disease(Orgeur et al., 2024). Whole-genome sequencing provides precise descriptions of mycobacterial genetic variation and has proved most useful for detection of antimicrobial resistance-associated mutations. It also differentiates between strains that circulate within a population, facilitates investigation of transmission dynamics, and detects evolutionary trends in the pathogen, which improves the ability to conduct epidemiologic and clinical surveillance (Xiao et al., 2023).

With regard to the host, genomic methods are used to study inherited factors that may affect the response to M. tuberculosis. Genetic polymorphisms that affect the detection of the pathogen, antigen processing, cytokine production, and immune regulation have been linked to altered susceptibility and disease outcome (Hoang Nguyen et al., 2025). However, susceptibility to TB is not influenced by a single genetic variant but rather by a combination of genetic, immunologic, and environmental factors. This limits the ability of a specific genomic marker to predict susceptibility(Smith et al., 2022).

Epigenomics provides additional information through investigation of regulatory mechanisms that control gene expression without changing the DNA sequence itself. Alterations in DNA methylation, histone modification, and chromatin structure can alter the gene expression profile of host immune cells during infection, affecting processes such as macrophage activation, inflammation, and immune memory (Zhang & Cao, 2021). Unlike genetic polymorphisms, epigenetic modifications are not inherited and may be modified by exposure to infection and other environmental conditions, leading to altered host immunity (Gopinathan & Diekwisch, 2022). Both genomics and epigenomics offer insight into the biology of TB, bridging inherited susceptibility with regulatory changes that occur during infection.

3.2 Transcriptomics and Single-Cell Transcriptomics

While genomics and epigenomics provide insight into the genetic background of disease susceptibility and epigenetic mechanisms of gene regulation, transcriptomics focuses on the dynamic processes of gene expression in response to infection(Shi et al., 2022). Bulk RNA sequencing allows for the simultaneous evaluation of thousands of transcripts, and has been employed to identify molecular pathways associated with disease progression, immune activation, and treatment outcome (Shi et al., 2022). Such studies have defined host gene-expression signatures associated with different clinical states of TB, and have informed the development of blood-based molecular biomarkers.

The clinical utility of transcriptomic profiling lies in its capacity to reflect systemic alterations in host immunity. The resulting transcriptional signatures can thus be used for disease classification, risk stratification, and monitoring of treatment response over time(Yan et al., 2025). However, bulk RNA sequencing data capture a composite signal from multiple cell types, which may mask biologically relevant differences between individual cell populations. Single-cell RNA sequencing overcomes this challenge by quantifying transcript abundance within individual cells. It has the potential to distinguish between different macrophage states, T-cell subtypes, and other immune populations involved in TB disease pathogenesis, providing a better characterization of the diversity of immune cells and the immune response(Huang et al., 2023). Resolving these differences, single-cell transcriptomics can provide clarity on the roles of individual cell populations in disease progression, inflammation, and clearing of infections. The impact of these results on the heterogeneity of cells and tissue-level organization is discussed in the

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

single-cell and spatial omics section(Wang et al., 2026).

3.3 Proteomics and Metabolomics

In addition to gene-expression changes, increasing attention has focused on proteins and metabolites, which provide a more direct representation of the functional consequences of molecular processes. Mass spectrometry-based proteomics allows the profiling of protein levels, modifications, and networks on a global scale (Hornisch & Piazza, 2025). In TB, proteomics has been used to identify host and pathogen proteins related to immune activation, disease status, and treatment response. This approach is also useful to explore the host–pathogen interactions at the cellular level. An understanding of these interactions can provide insights into how M. tuberculosis manipulates host cell pathways for intracellular persistence and identifies potential drug targets. Finally, protein signatures can help contextualize genetic and transcriptional profiles by providing information about ongoing functional events(Hu et al., 2025).

Metabolomics, similarly, can be used to profile the small molecules generated or consumed by biological processes. TB infection is characterized by significant metabolic changes in both the host and the pathogen(Qiu et al., 2023). Immune cells activated during the course of TB infection must undergo metabolic reprogramming to sustain their functional requirements, while M. tuberculosis alters its metabolism to adapt to its dynamic environment within the host. Changes in metabolism might be correlated with features such as disease severity, degree of inflammation, or treatment response. With the increasing recognition of immunometabolism as an important determinant of immune cell function and thus immunity versus pathology, proteomics and metabolomics could prove critical to understanding how biological events impact TB pathogenesis, particularly when integrated with genetic and transcriptomic information(Warner et al., 2025).

3.4 Lipidomics and Microbiome Research

Another important facet to TB research is lipidomics. Lipids play a major role in M. tuberculosis physiology and host response to infection. The mycobacterial cell envelope has many types of lipids involved in pathogenesis, immune evasion, and bacterial survival(Radhakrishnan & Sundaramurthy, 2026). Host lipid metabolism is also altered during infection, specifically in macrophages and granulomas, which could impact intracellular survival or inflammatory signaling. Analysis of lipids may further elucidate metabolic interplay in host-pathogen interactions(Kim & Shin, 2023).

Microbiome studies may provide yet another perspective by exploring how commensal microbes may regulate immunity and disease susceptibility. The gut-lung axis suggests that intestinal flora and metabolites might influence pulmonary immune function (Kamel et al., 2024). While the microbiome's role in TB is still being explored, microbiome-immune interactions might explain differences in host responses and add another layer to understanding disease variability(Mori et al., 2021).

3.5 Multi-Omics Integration and Systems Biology

The true value of multi-omics is not merely in collecting huge volumes of molecular information, but in integrating this complementary information to improve our understanding of disease(Sibilio et al., 2025). Different omic layers capture different aspects of biological processes: genomics detects genetic variants; epigenomics captures changes in gene regulation; transcriptomics reflects transcriptional activity; proteomics assesses the abundance of proteins that exert functions in the cell; and metabolomics and lipidomics provide information on cellular physiology. Multi-omics data integration, via data fusion, enables researchers to investigate relationships between these different omic layers in combination(Shafqat Rasool, 2026).

The integration of data from multiple omic layers can form a systems biology framework to identify networks, pathways, and interactions that govern disease in tuberculosis. For instance, this can involve linking genetic variation with gene expression, protein networks, metabolism, and clinical parameters(Alam et al., 2022). Systems biology is particularly useful for host–pathogen

Frontier in Medical & Health Research

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interaction studies because multiple interacting processes contribute to disease in tuberculosis. Systems immunology further integrates data to better understand the immune response, by considering immune cells, signaling pathways, and molecular mediators as components of a network. Instead of investigating individual cytokines or immune cell types, this approach could identify complex interactions related to effective protection, pathology, or treatment(Borah et al., 2021).

An important feature of multi-omics data integration is the potential to generate multi-layer signatures. Information derived from multiple data types may better characterize disease compared to a single biomarker. This could also help differentiate patients with the same clinical presentation based on underlying molecular features. These capabilities set the stage for novel approaches to classifying and grouping patients, which could further guide the implementation of precision medicine in TB research(Alam et al., 2022). However, data integration poses many challenges given the complexity of analyzing multiple high-dimensional datasets. Finding relevant signals from multi-omics data necessitates sophisticated computational methods to uncover relationships among diverse types of variables. This motivates the final section of this review that describes how artificial intelligence and machine learning can assist with the integration and analysis of multi-omics data in tuberculosis (Yetgin, 2025).

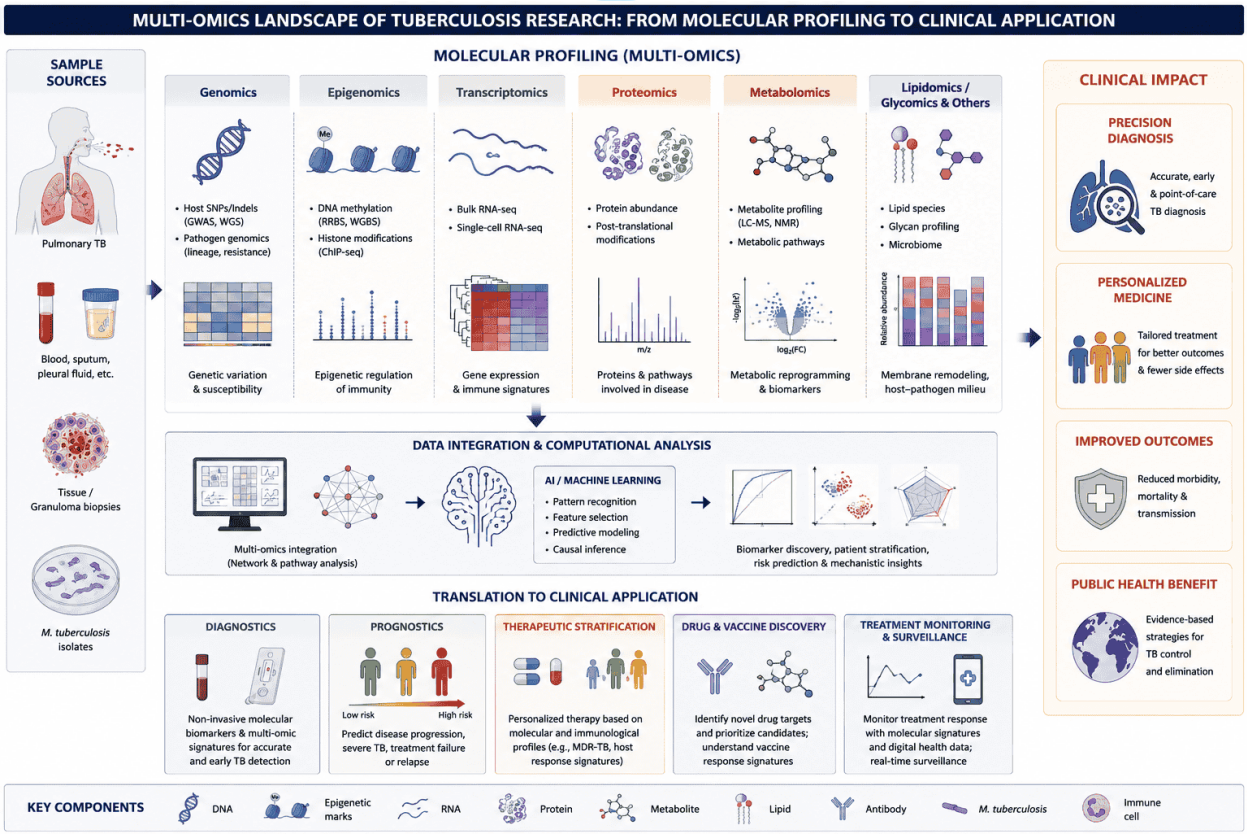

Figure 2. Multi-omics landscape of tuberculosis research from molecular profiling to clinical application.

Multiple omics technologies provide complementary information on host susceptibility, immune responses, pathogen adaptation, and disease-associated molecular changes. Integration of genomic, epigenomic, transcriptomic, proteomic, metabolomic, lipidomic, and microbiome data enables systems-level characterization of tuberculosis, facilitating

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

biomarker discovery, patient stratification, disease prediction, personalized treatment, and treatment monitoring. Together, these approaches provide a molecular foundation for the transition toward precision tuberculosis.

4. Artificial Intelligence in Tuberculosis Research

The growth of multi-omics technologies has resulted in increasingly complex data that cannot be interpreted using traditional methods alone. In the context of tuberculosis, disease outcomes result from a combination of host genetic makeup, host immunity, pathogen factors, clinical variables and environmental exposures (Carabalí-Isajar et al., 2023). Artificial intelligence (AI) and machine-learning approaches provide a means of identifying patterns within complex, heterogeneous datasets and linking molecular data to clinically relevant outcomes(Wei et al., 2023).

Rather than replacing traditional biology or clinical research, AI offers ways to complement these methods and to help translate high-dimensional data into interpretable and potentially useful knowledge(Wilson & Anwar, 2024).

4.1 AI for Multi-Omics Integration

One of the challenges in multi-omics research is the need to integrate the information derived from these different biological layers. The genomic, transcriptomic, proteomic, and metabolomic data differ in terms of the size, structure, and biological significance of the measurements they contain, and it is therefore difficult to study how these datasets relate to each other using basic descriptive techniques(Luo et al., 2024). Machine-learning approaches can address this challenge by detecting patterns within and between datasets and selecting combinations of molecular features that correlate with disease states or clinical phenotypes(Rashid & Selvarajoo, 2024).

Supervised methods, for instance, can take existing disease states, such as active vs. latent infection or responders vs. non-responders to treatment, and use these known groups to learn which biomolecular features predict these outcomes(Nguyen et al., 2021). Unsupervised methods, on the other hand, do not require prior knowledge about the underlying structure of the data and can be used to discover novel patient subgroups or biological states. Finally, deep-learning approaches could be useful for modeling the intricate, nonlinear relationships between the diverse data types that are typically collected in TB studies(K.B et al., 2025).

Feature selection is particularly relevant in TB multi-omics research, where the number of molecular variables often exceeds the number of available samples. Computational approaches can prioritize informative genes, proteins, metabolites, or combinations of features, reduce dimensionality, and retain biologically relevant information. These data can then be integrated with clinical, imaging, and demographic variables to provide a more comprehensive representation of disease heterogeneity(Curion & Theis, 2024).

4.2 AI-Driven Biomarker Discovery

Another key area of TB research is biomarker discovery. TB is biologically and clinically very heterogeneous, and therefore single biomarkers may not be as useful for diagnosis or prediction(Perumal et al., 2021). Multiple features can be assessed by AI simultaneously to identify signatures that could potentially be used for predicting disease state and outcome (Al-Ewaidat & Naffaa, 2025).

For example, a signature could help distinguish between patients with active TB and patients with other clinical presentations, whereas a prognostic signature might be used to identify people at higher risk for bad outcomes or disease progression. Molecular signatures associated with treatment response could potentially help identify early which individuals will have a poor response to treatment. Moreover, AI-based models could also integrate molecular and clinical data for risk stratification and individualized prediction of disease progression, treatment failure, or relapse. However, such models should be validated, reproducible, and generalizable across diverse genetic and healthcare environments to be effective(Javaid et al., 2025).

4.3 AI in Tuberculosis Diagnosis

Frontier in Medical & Health Research

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Aside from molecular diagnostics, one area where AI has received significant interest is in processing diagnostic information, especially in imaging, such as chest X-rays. Machine-learning and deep-learning algorithms can analyze chest images and identify patterns associated with pulmonary TB (Al-qaness et al., 2024). This technology could be used for mass screening and aid clinical services in areas where there is a lack of highly skilled radiologists, by providing faster and more uniform results in interpreting the images (Sharma et al., 2024).

AI tools can also be applied to processed data from computerized tomography scans (CT scans), which are capable of detecting intricate structures in a patient. Although CT scans are not generally available and too costly, they represent an important potential use of AI-based diagnostics for TB(Paudyal et al., 2023). More importantly, information generated from imaging techniques, when combined with other available molecular, microbiological, clinical and laboratory information, could potentially enhance classification and further aid clinical decision-making(Sande & Rajguru, 2025). AI-based diagnostics should not be seen as a substitute for molecular and microbiological diagnostics, but rather as a means of decision support, which, together with these approaches, will facilitate more accurate diagnosis (Talianu et al., 2026).

4.4 AI for Drug Discovery and Host-Directed Therapy

There is a growing trend in using AI tools to speed up the search for novel therapies against TB. The use of genomic, transcriptomic, proteomic and network data can be utilized to create computational models which can then pinpoint pathways within the bacteria or host cells that are important in determining bacterial survival, disease outcome or response to therapy(Sharma et al., 2025). These techniques can help to prioritize putative drug targets and suggest new hypotheses to test experimentally. Furthermore, AI approaches can facilitate drug repurposing by enabling the systematic screening of known drugs, thus revealing which candidates might exhibit anti-M. tuberculosis activity, or target host pathways related to disease (Melamane et al., 2023). Finally, AI methods can assist with prioritizing candidate drugs through virtual screening or predictive modeling, again prior to conducting expensive laboratory and clinical studies(Dermawan & Alotaiq, 2025).

In addition to targeting the pathogen itself, AI could potentially facilitate the identification of pathways within the host that are associated with bacterial persistence, disease severity or suboptimal response to treatment, which could then inform host directed therapies. These discoveries could be combined with the detailed molecular and clinical data available for each patient to provide personalized approaches to treatment. Nevertheless, these strategies would need to be extensively validated experimentally to prove their clinical relevance (Yakobi & Nwodo, 2025).

4.5 Explainable and Trustworthy AI

Although there are opportunities for the use of AI in TB research and clinical care, it comes with important methodological and ethical considerations. First, complex machine-learning models are difficult to interpret. Even when highly predictive, an algorithm may not clearly indicate which factors contribute most to a particular prediction (Tursunalieva et al., 2024). To overcome the black-box nature of these algorithms, explainable AI techniques may be used to highlight the features that most influence the predictions, which may facilitate understanding of the biological and clinical implications (Qadri et al., 2025).

The second important consideration is that predictive algorithms themselves are subject to bias. Models that are trained on small, biased, or non-representative sample datasets might fail to perform adequately in populations with distinct genetics, disease phenotypes, or healthcare resources. TB primarily occurs in low- and middle-income countries, where these data types are less commonly collected and used to train advanced predictive algorithms. Models should be independently tested in diverse populations and clinical settings before being implemented in patient care (Kumar & Roy, 2025).

Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Additionally, data privacy, consent, equity, accountability, and governance concerns should be addressed to facilitate responsible AI implementation. For AI to positively impact precision TB, its models must be accurate, transparent, replicable, clinically validated, and generalizable. The future success of AI in TB will require strong basic science coupled with effective implementation. When combined with large-scale omics data and appropriate validation, AI can help advance personalized and equitable precision TB medicine(Filho et al., 2025).

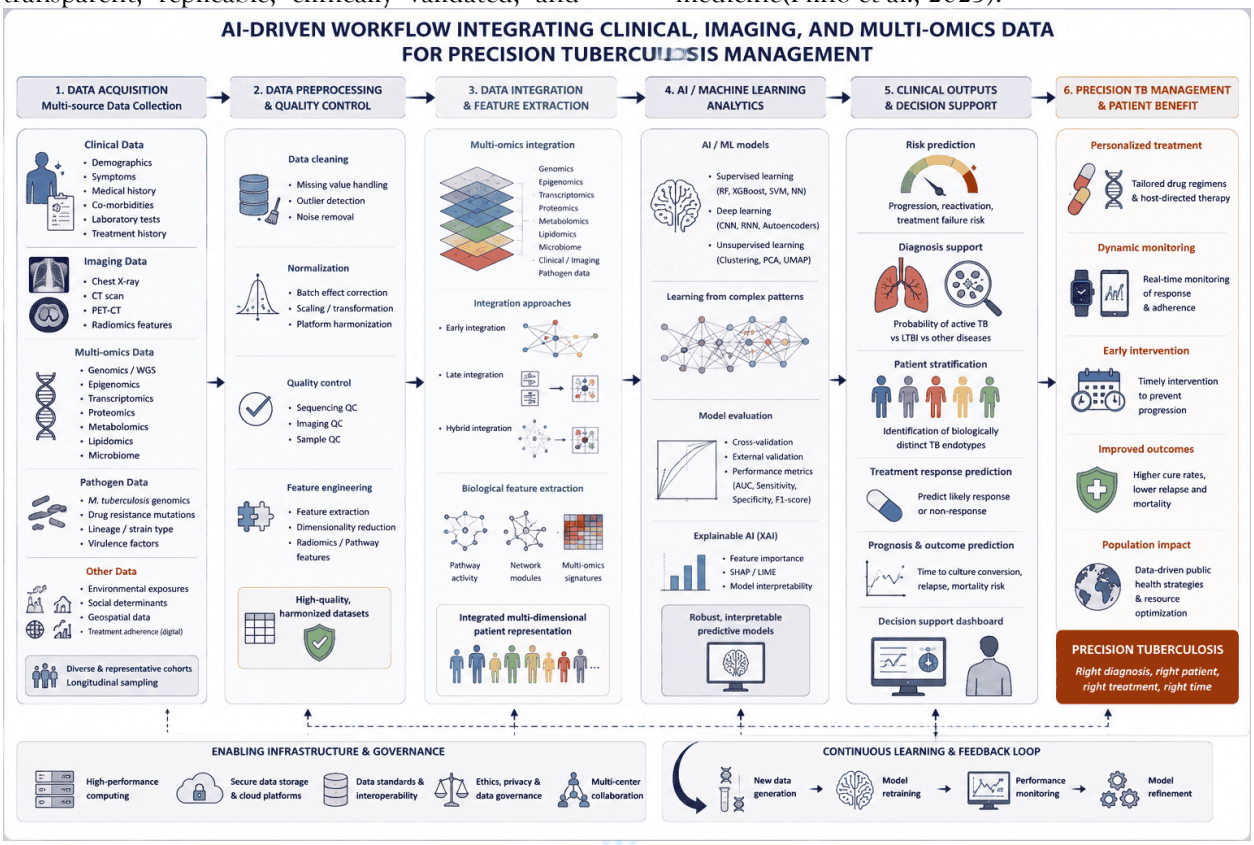

Figure 3. AI-driven workflow integrating clinical, imaging, and multi-omics data for precision tuberculosis management

Preprocessing, quality control, and feature extraction are performed on clinical, imaging, pathogen, and multi-omics data, followed by multimodal integration with machine learning and deep learning methods. Such data-driven models can be used for diagnosis, risk prediction, patient stratification, treatment response evaluation, and prognosis. These data-driven insights may also facilitate evidence-based clinical decisions, individualized treatment plans, continuous patient monitoring, and early interventions, ultimately paving the way toward precision tuberculosis.

5. Single-Cell and Spatial Omics: Resolving TB at Cellular Resolution

Despite the value that bulk omics have provided to the field of TB research, these approaches tend to report averaged molecular profiles across mixed populations of cells. This means that relevant biological differences among immune cells and their microenvironments can be masked. Single- and spatial omics can address this issue by analyzing molecular heterogeneity in more detail while also retaining information about the composition and arrangement of cells in tissues. These attributes make them especially useful for investigating TB, as the disease develops through

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

dynamic interplay among multiple immune cell types in structures like granulomas(Baysoy et al., 2023).

5.1 Cellular Heterogeneity During TB Infection

There is significant heterogeneity among the immune cells present in TB infections. For example, macrophages represent the major intracellular niche for M. tuberculosis but are not a monolithic cell population. Different macrophage populations may exhibit distinct activation states, metabolic programs, antimicrobial capacities, and varying abilities to support bacterial survival. Some could be more protective while others could promote the establishment of infection (Pisu et al., 2021). In addition, CD4+ and CD8+ T cells can assume different functional states depending on variations in antigen load, inflammation, and the tissue microenvironment. Persistent antigenic stimulation may lead to altered T-cell function and immune exhaustion. Therefore, protective and detrimental immune responses could be present simultaneously in the same infected tissue, and defining the immune response to TB only as a population of certain cell types becomes challenging(W. Jiang et al., 2021).

In addition, single cell technologies enable the study of cellular lineages and transitions of immune cells to different functional states throughout the course of infection. These studies can elucidate the mechanisms underlying activation, differentiation, dysfunction, and/or recovery. It may also be possible to understand why patients with similar symptoms can have different immune responses and clinical outcomes (Ginhoux et al., 2022).

5.2 Single-Cell Multi-Omics

Single-cell RNA sequencing (scRNA-seq) is widely used to characterize gene-expression profiles of individual cells. It has been applied in TB research to identify distinct immune-cell populations and uncover transcriptional programs associated with infection, inflammation, and immune regulation(Jovic et al., 2022).

However, transcriptional activity is only part of what defines cellular function. Integrating complementary single-cell technologies yields a more complete understanding of cellular biology. Single-cell ATAC sequencing (scATAC-seq), for instance, provides information about chromatin accessibility and helps identify the regulatory program that dictates a given cell state (Wang et al., 2025). CITE-seq measures both transcriptomic and cell-surface protein levels, enhancing the resolution of immune-cell phenotypes. Multiomics techniques also enable researchers to profile several molecular layers, including both gene expression and chromatin accessibility, from a single cell (Sahu et al., 2025).

These techniques can be combined to link cell identity with its underlying regulatory program and functional state. In the case of TB, single-cell multi-omics can help reveal which specific immune-cell states are related to control of bacteria, disease progression, or variation in treatment response. Rather than simply studying large groups of different types of immune cells, single-cell multi-omics gives researchers a way to study the molecular programs that define specific cell states (Liang et al., 2024).

5.3 Spatial Omics and Granuloma Biology

Despite its high resolution, most single-cell studies rely on tissue dissociation, losing information about the spatial organization of the tissue. Spatial omics methods aim to retain the spatial information of cells and molecules in the tissue. This is especially useful for studying TB, in which the granuloma is a structured, highly heterogeneous site, rather than a homogeneous pool of immune cells.

Spatial methods may show how macrophages, lymphocytes, and other immune cells are organized in the granuloma, and how their function differs by location. The local microenvironment may differ based on inflammation, metabolism, and antimicrobial activity, all of which may affect bacterial survival and disease outcomes. Spatial methods also enable the investigation of host–pathogen interactions through the examination of spatial proximity and potential communication between cells. Integrating spatial data with ligand–receptor analysis and other omics data can help elucidate

Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

how spatial organization and proximity among cells influences the coordination of protective immunity and/or bacterial survival and pathology (Qiu et al., 2024).

Integrating single-cell and spatial methods with other omics data could provide a multi-scale view of TB across the molecular, cellular, and tissue levels. It could also bridge the gap between mechanistic studies of host–pathogen interactions and clinical insights, as it may reveal disease-relevant cell states and tissue-specific molecular signatures that are not captured by bulk analyses (Jiang et al., 2025).

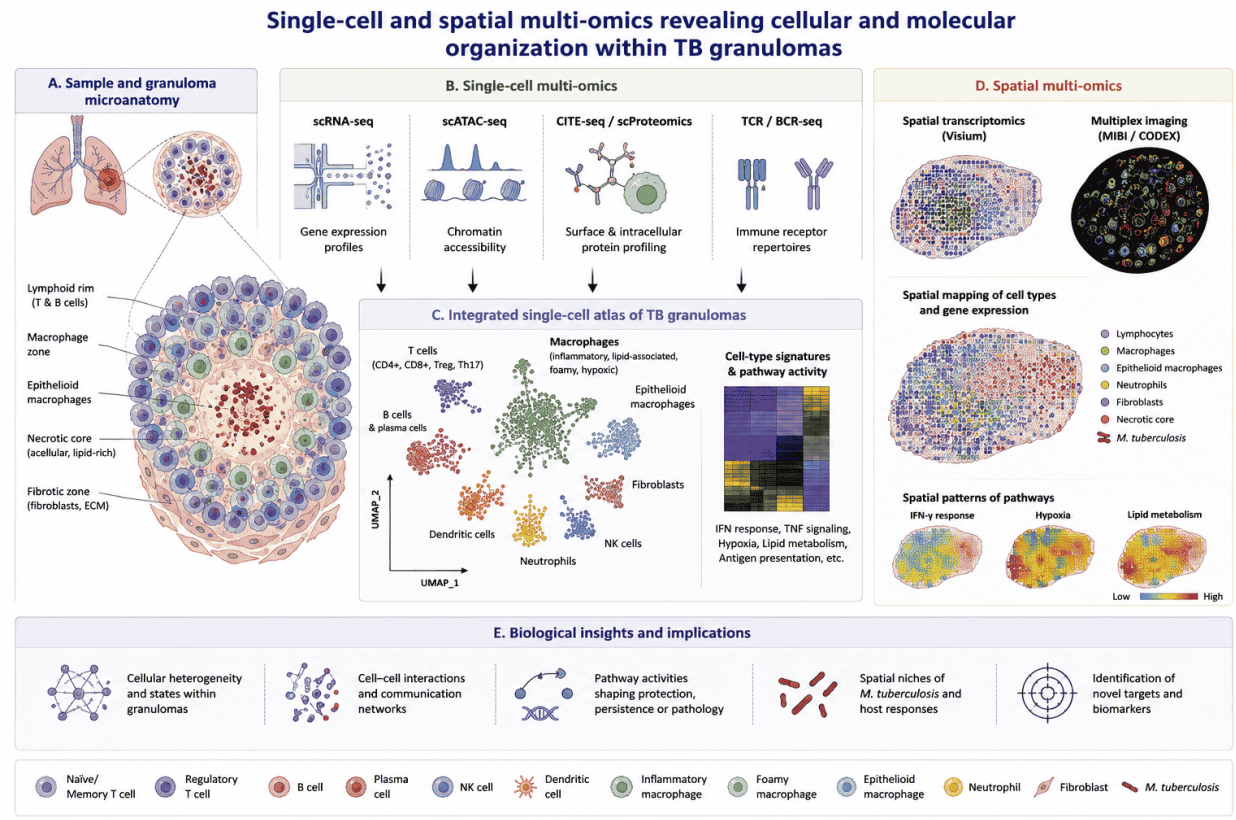

Figure 4. Single-cell and spatial multi-omics revealing cellular and molecular organization within TB granulomas

Single-cell approaches resolve the diverse immune and stromal cell populations, transcriptional states, regulatory programs, and cellular trajectories associated with tuberculosis. Spatial multi-omics complements these analyses by preserving tissue architecture and revealing cellular niches, gene-expression patterns, and cell–cell interactions within granulomas. Together, these technologies provide a high-resolution view of the cellular and molecular organization underlying bacterial persistence, host defense, and TB pathogenesis.

6. From Multi-Omics to Precision Tuberculosis

Incorporating multi-omics and informatics tools to study tuberculosis will help to shift the paradigm from a population-based to a patient-centric disease management approach. Patients with TB vary considerably in their genetic predisposition, immune response, disease course, pathogen features, and treatment outcomes (Stanley et al., 2022). A one-size-fits-all approach might not capture the complex biology that contributes to these variations. The aim of precision tuberculosis is to harness multi-modal data including molecular, immunological, microbiological, clinical, and (more recently)

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

digital sources to define TB at the individual level. It holds the promise to improve diagnostic and prognostic accuracy through recognition of biologically distinct TB phenotypes and clinically meaningful molecular signatures (Dartois & Rubin, 2022).

6.1 Personalized Diagnosis and Biomarker-Guided Testing

TB diagnosis is currently based on microbiological identification, molecular tests, radiography, and clinical assessment. Although these are important, they do not always account for the molecular and immunological diversity that exists between different stages of disease, or disease presentations. The advent of multi-omics offers an opportunity to supplement current diagnostic approaches by determining a pattern of biomarkers that reflects disease activity, host response, and other biologically significant factors (Mohr et al., 2024). There is evidence of transcriptomic, proteomic, and metabolomic differences between active disease, latent infection, and treatment response. It is likely that the combination of multiple molecular features will be of greater diagnostic utility than a single biomarker, especially in a biologically diverse disease such as TB (J. Jiang et al., 2021).

These signatures could inform biomarker-directed testing, providing additional information alongside current microbiological and clinical assessments. In future, personalized diagnosis may require evidence of infection in conjunction with a molecular profile derived from the host. Machine learning approaches could further facilitate this by combining complex biomarker signatures with clinical and demographic data to improve patient stratification and promote a more biologically driven diagnostic strategy(Parvin et al., 2025).

6.2 Prediction of Disease Progression and Reactivation

The question of which infected individuals will develop active TB is an important area of study. Disease exists on a continuum, and the standard dichotomous classification of TB infection does not explain why some individual's control infection whereas others develop progressive disease or reactivation (Abubakar et al., 2026).

Multi-omics offers an avenue to identify the molecular changes associated with this continuum. Changes to gene-expression, immune responses, metabolism, and other biological processes could reflect earlier changes that lead to disease (Feya et al., 2026). Host transcriptional signatures may capture changes in the immune response that reflect progression to active disease, and integrated molecular profiles might be able to capture features that differentiate those with differing risks of progression or reactivation (Starshinova et al., 2025).

AI can complement such approaches by identifying associations between these molecular and clinical, demographic, and even potentially environmental features. By combining risk factors rather than considering each one in isolation, machine-learning models can capture more complex relationships between features, leading to better risk predictions. These models can then be used to monitor and provide targeted preventive measures for those at risk of progression or reactivation. As with any predictive model, further validation will be necessary before its implementation in clinical care, especially in regions with a high TB burden (Westerlund et al., 2021).

6.3 Personalized Treatment and Host-Directed Therapy

Most TB treatments are currently standardized regimens, but patients differ greatly in bacterial features, immune response, metabolism, and treatment outcome. Precision medicine attempts to address such diversity by grouping patients based on clinically relevant categories that might have a distinct response to treatment (Wang & Wang, 2023). For example, multi-omics analysis could identify phenotypic markers linked to disease severity, disease activity, or treatment response. Some patients might present with a highly inflammatory phenotype, while others may display a suppressed or altered metabolism phenotype, for instance. Identifying these groups may help determine which patients are more likely

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

to benefit from adjunctive treatment (Linz et al., 2025).

This is especially true for host-directed therapy, which involves modulating host mechanisms related to immune modulation, inflammation, tissue damage, or bacterial persistence, for example. Multi-omics data analysis could help identify potential pathways for this type of therapy and help elucidate the biology behind different disease phenotypes. These insights would allow us to move away from an "one size fits all" approach where the same host-directed agent is added to the standard treatment regimen, instead towards selecting an appropriate host-directed therapy based on individual's molecular and immunological profile (Ivanisevic & Sewduth, 2023).

Using artificial intelligence techniques, it may also be possible to combine molecular signatures with microbiological and clinical data to predict response to treatment. AI models might allow us to detect individuals who are at higher risk of treatment failure or relapse earlier and therefore enable enhanced surveillance or modification of the therapeutic plan. This type of strategy will require strong biological plausibility and clinical validation to translate to clinical practice (Behera et al., 2025).

6.4 Precision Vaccines and Immune Correlates of Protection

One major barrier to TB vaccine development is that the nature of protective immune responses against M. tuberculosis has not been comprehensively characterized. By analyzing immune responses at multiple levels simultaneously, multi-omics can be used to determine how gene expression, immune-cell phenotype, protein abundance, and metabolism vary in individuals who are protected or susceptible to TB infection (Chu et al., 2021).

These systems-level analyses can be used to uncover immune correlates of protection by identifying differences in molecular and cellular signatures between individuals experiencing different clinical outcomes. Additionally, single-cell and spatial-based approaches could be used to determine which immune cell states, transcriptional programs, and tissue-localized immune interactions are critical for controlling mycobacterial infections (Geraldes et al., 2022).

Characterizing immune markers of vaccine responsiveness could help researchers define the features of vaccine-induced immunity in specific populations. This approach would also allow researchers to stratify participants based on their immunological characteristics in order to tailor vaccines to specific groups. Artificial intelligence could be used to analyze large-scale immunological datasets and identify molecular and cellular signatures predictive of vaccine-induced protection (Kumar et al., 2026). While precision vaccination is still a nascent idea in TB, utilizing multi-omics and artificial intelligence could allow researchers to improve the selection and assessment of candidate vaccines.

6.5 Monitoring Treatment Response

Precision approaches can also be used to monitor therapeutic response. Traditional microbiological testing and clinical assessment remain key to the management of TB, but these might not necessarily yield an early or complete picture of the biological changes that occur during therapy (Song et al., 2025). Transcriptomic signatures could provide useful information about changes in host immune responses and the clearing or maintenance of disease-related inflammation, while metabolomic signatures could reveal changes in host physiology and metabolism. Combining molecular measures with clinical observations could identify patients who exhibit a discordant response between their biology and clinical state (Rahimpour et al., 2024).

In addition, digital biomarkers derived from imaging, wearable technologies, or longitudinal clinical datasets could be integrated with molecular, microbiological, and clinical data using AI models to provide a more dynamic assessment of therapeutic response and improve outcome prediction. Molecular and digital techniques could therefore transform the monitoring of therapeutic response from a standardized approach to one that is individualized to the patient (De Deo et al., 2025).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

However, numerous challenges still need to be overcome, such as biomarker standardization, cost of analyses, clinical validation, and the translation of this work to high-burden settings. Ultimately, the shift from multi-omics research towards precision TB requires the conversion of multi-dimensional biological data into actionable clinical decision-making. The goal is not just to generate increasingly complex molecular portraits, but to use the information obtained to improve diagnostic accuracy, detect patients at risk of disease progression, personalize therapeutic interventions, monitor therapeutic response, and aid in the design of better vaccines (Starshinova et al., 2026).

Table 2: Clinical Applications of Multi-Omics and AI in Tuberculosis

Clinical Area	Technology	Example Application	Translational Status
Diagnosis	Transcriptomics + ML	Blood-based signatures	Emerging
Drug resistance	Genomics + AI	Resistance prediction	Developing
Risk prediction	Multi-omics	Progression prediction	Research
Treatment monitoring	Proteomics/metabolomics	Response assessment	Emerging
Drug discovery	AI	Drug repurposing	Research
Precision therapy	Multi-modal data	Patient stratification	Future

7. Emerging Technologies and Future Directions

The integration of multi-omics and AI is broadening the range of experimental and analytical approaches that are available to study tuberculosis. While existing methods have significantly advanced our understanding of host–pathogen dynamics, there remain significant translational barriers between molecular insights and clinical practice (Behera et al., 2025). Newer technologies could help overcome some of these challenges, allowing scientists to transition from identifying markers of disease to functionally interrogating mechanisms, using more physiologically relevant models of human infection, and generating predictions about disease outcomes on a per-individual basis (Rasool et al., 2026).

In particular, functional genomics, innovative disease models that closely recapitulate aspects of human TB, and AI-based analytical frameworks hold promise in this respect and could enhance the link between mechanistic discoveries and precision TB by improving models of host–pathogen interactions and by developing more sophisticated tools for predicting TB trajectories and treatment outcomes (Muhammad et al., 2025).

7.1 Functional Genomics and CRISPR

Unlike other omics studies that focus on discovering genes linked to disease, functional genomics aims to define the function of those genes. While genomic and transcriptomic analyses can uncover genes associated with susceptibility, disease severity, or therapy response, they cannot determine which of these genes actually play a functional role in host immunity or bacterial viability (Liu & Song, 2025).

CRISPR-based functional genetic approaches in *M. tuberculosis* could identify genes important for virulence, metabolism, persistence, and drug resistance. Likewise, CRISPR-based screens in host cells could identify host genes and pathways that are involved in bacterial uptake, survival within host cells, immune activation or inflammation. Combining CRISPR-based functional screens with transcriptomics and other omics data could facilitate the discovery and confirmation of relevant biological processes rather than simple correlations, thus expediting the discovery of therapeutically relevant targets and enabling more effective design of pathogen- and host-directed therapies (Rasool et al., 2026).

7.2 Advanced TB Models: Organoids and Lung-on-a-Chip Systems

Although traditional cell culture and animal models have yielded valuable insights into TB pathogenesis, they cannot fully recapitulate

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

human infection. Newer experimental systems such as organoids and organ-on-a-chip systems provide more physiological settings for studying host–pathogen interactions (Baddal & Marrazzo, 2021).

Lung organoids recapitulate certain structural and cellular features of human lung tissue in a 3D setting, providing the possibility to study epithelial–immune crosstalk, tissue-specific responses and factors contributing to bacterial survival in more physiologically relevant settings than those available using traditional 2D cell culture. Similarly, lung-on-a-chip models utilize microfluidics to recreate certain aspects of lung tissue architecture, biomechanical forces, and cellular dynamics, enabling researchers to study the temporal course of infection, inflammation, tissue damage and treatment responses in controlled settings (Joo et al., 2024).

Together with multi-omics approaches, these novel systems can provide molecular-level information in highly controlled and relevant biological systems, potentially allowing for more detailed mechanistic research, facilitating preclinical drug development and reducing some of the drawbacks of traditional models.

7.3 Digital Twins and Computational Modeling

Yet another avenue of exploring the complexity and dynamics of TB is computational modeling. Mathematical and computational models combine data about bacterial growth, host immune responses, drug exposure, and disease course to determine how these parameters affect each other over time (Franco & Rezzani, 2024).

Digital twins a virtual representation of a biological system or individual that is continually updated with new experimental, molecular, and clinical data build on this concept. In the future, a digital twin of a TB patient could reflect host immune features, pathogen features, multi-omics information, radiographic findings, and serial measurements of treatment exposure and response (Katsoulakis et al., 2024) .

These types of models might enable simulation of disease trajectories and evaluation of individual responses to various treatment strategies. Computational models could consider the dynamics of the bacterial population, the immune response, drug exposure, and the impact of changes in treatment plan before applying them to patients (Jenner et al., 2020). While a patient-specific digital twin does not yet exist for TB, existing computational models are still useful tools to study complex biological dynamics. Larger longitudinal and multimodal datasets will make such approaches even more valuable in predicting outcomes of disease and optimizing individualized treatment strategies (Laubenbacher et al., 2024).

7.4 Federated Learning and Global TB Data

One major barrier to building effective and broadly applicable models is that biomedical data remain confined to single institutions, countries, or health systems. This is especially true for TB, where high-burden populations are geographically scattered and often have distinct genetic profiles, phenotypes, health systems, and data policies that may limit centralized data-sharing and lead to AI models being trained on small or narrow datasets (Zhang et al., 2022).

Federated learning offers a way around this issue, allowing machine learning models to learn from data held across many institutions without requiring direct data transfer, instead exchanging trained model parameters or model updates. For TB, it could enable data-sharing across cohorts from different locations and the development of larger, more representative datasets. It would also allow the integration of clinical, radiological, microbiological, and genomic data from diverse high-TB-burden settings while ensuring adherence to data privacy, ownership, and governance requirements. However, its implementation will require agreement on standards, interoperability, governance, and equity (Yurdem et al., 2024).

7.5 Toward Multimodal Foundation Models for Infectious Diseases

Another emerging direction is the development of multimodal foundation models trained on several different types of biomedical data, as opposed to data from one specific type of analysis. Such models may be trained on exceptionally large and varied data sets, and subsequently fine-tuned to perform multiple downstream tasks. These models

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

may use multiple data modalities, including genomic and transcriptomic data, proteomics, medical images, clinical notes, and biomedical text (AlSaad et al., 2024).

In TB, multimodal models could help integrate our knowledge of molecular and cellular mechanisms and clinical phenotypes. For instance, a model could combine chest imaging, host molecular markers, M. tuberculosis genomic data, immune profiles, and clinical information to aid in TB diagnosis, risk stratification, assessment of treatment efficacy, and other precision medicine applications (Yang et al., 2026).

Developing such multimodal models poses many challenges. Their implementation will depend on the existence of sufficiently large, diverse, and high-quality data sets, as well as proof of transparency, biological interpretability, external validity, and applicability in real-world clinical contexts. Moreover, such models should not perpetuate global health inequities by only training on small subsets of patients and resource-rich settings (Liu et al., 2025).

Ultimately, these developments indicate a shift away from individual experimental and computational methods toward more integrated models of TB biology. Functional genomics can uncover causal biological pathways, better tissue models can offer more biologically relevant platforms for modeling disease, and joint computational analyses can unite molecular and clinical data. Together, these efforts could lead to more predictive and personalized models of TB, but their translation into the clinic will require addressing many technical, biological, ethical, and practical challenges (Cano-Gamez & Trynka, 2020).

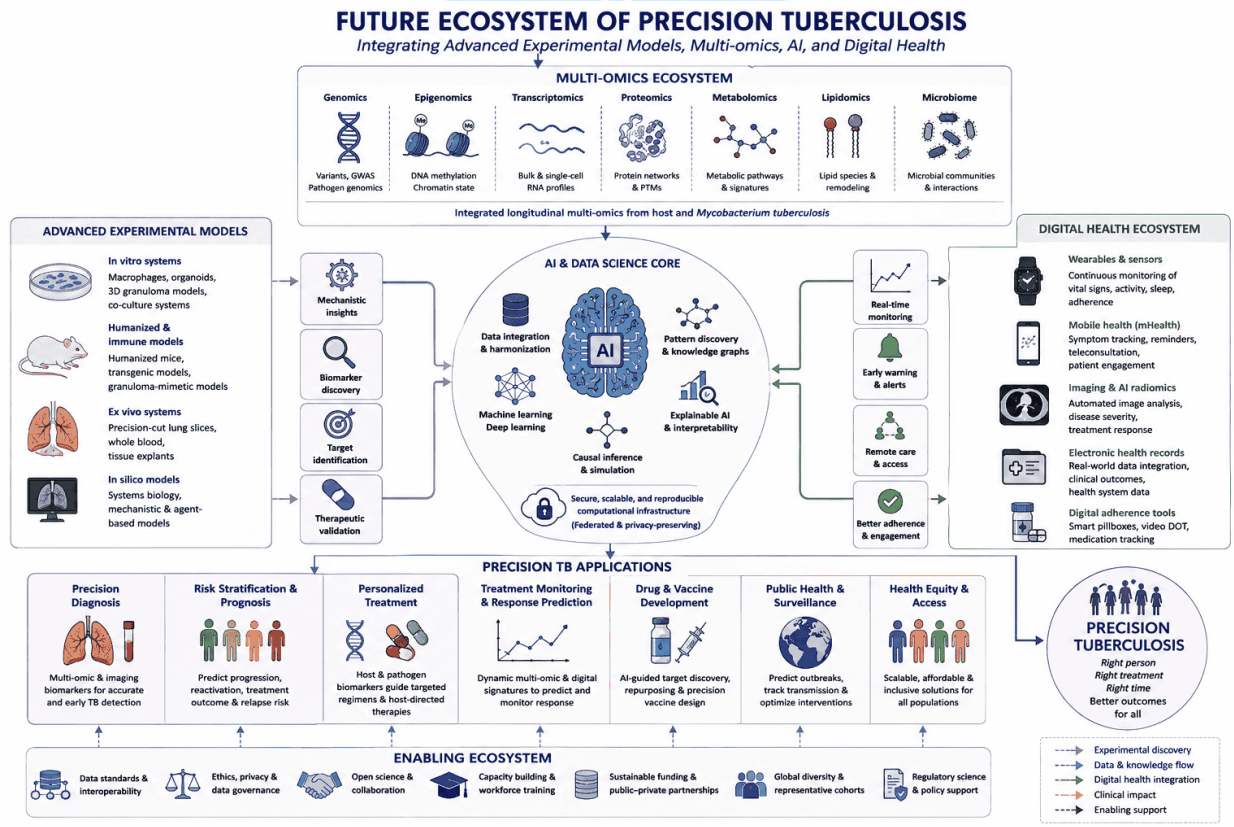

Figure 5. Future ecosystem of precision tuberculosis integrating advanced experimental models, multi-omics, artificial intelligence, and digital health.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

These emerging experimental platforms, molecular profiling tools, analytical methods, and clinical data streams can be combined to develop an iterative, evolving picture of TB on the molecular, cellular, and patient scale. The synergy of these diverse systems could enable more accurate diagnostic and prognostic tools, clinical stratification, precision medicine, and adaptive monitoring if issues of clinical validation, data management, compatibility, and access can be resolved.

8. Challenges and Barriers to Clinical Translation

While there has been tremendous expansion in multi-omics and artificial intelligence (AI), their translation into clinical TB practice remains difficult. A major challenge is not only to generate high-resolution molecular data, but also to ensure that they can be replicated, used to make decisions, and generalized to different populations and settings (Mendes et al., 2025).In addition, TB is influenced by the complex interactions between the host, pathogen and environment, and the technology used to study these interactions adds complexity. It is important to address these challenges to enable the effective translation of molecular and computational discoveries for TB diagnosis, treatment, and prevention (Franco & Rezzani, 2025).

8.1 Biological and Technical Challenges

The biology of TB is heterogeneous, and clinical features are affected by a variety of factors including host genetics, immune function, comorbidities, infecting M. tuberculosis strains, stage of disease and environment. These differences make it challenging to identify consistent molecular markers, and may also affect how well findings from one population translate to another (Chung et al., 2022).

Another significant challenge is that experimental techniques used to obtain and analyze samples vary, including sample collection, preparation, storage, sequencing platform and analysis. These technical differences can affect omics data. The small sample size, typical of high-dimensional studies, can reduce the power of analyses and limit how generalizable study findings are. Furthermore, batch effects can contribute additional variation, obscuring the biological signal. To address these challenges, researchers will need to continue to standardize methods throughout the process, from study design, sample collection, processing and analysis to data generation, QC and reporting. It will also be critical to generate larger, more diverse and well-characterized cohorts to identify more reliable markers and determine whether they can be applied beyond the specific cohorts in which they were identified (Bharti & Grimm, 2021).

8.2 Computational and AI Challenges

Another significant hurdle associated with multi-omics data integration is the fact that different platforms generate data with different characteristics, ranges, and biology. The presence of missing data, variable quality of data and relatively small sample size make finding robust cross-domain associations even more difficult (Chen et al., 2025).

A further complication brought about by AI-based models is the possibility of overfitting in cases where large numbers of molecular features are being studied in a small number of patients. A machine learning model is considered to have been overfitted when it accurately predicts outcomes for the patients used in training but fails to accurately reproduce these findings when tested in another cohort of patients. Therefore, before AI can be used to inform clinical decision-making, it must first be appropriately validated and tested in several independent populations (Zehra et al., 2026).

A final concern regarding machine learning models is bias. If the data that were used to build the model do not accurately reflect the populations that are most likely to develop TB, then the predictions made by the model will be inaccurate and/or inequitable. Additionally, some complex machine learning models are difficult to interpret, meaning it will not be clear which clinical and/or molecular variables contributed to any particular prediction. Better understanding of how and why predictions are made will help foster clinical confidence and enhance our ability to

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

determine whether the relationships identified by AI are meaningful (Barbierato & Gatti, 2024).

8.3 Clinical, Ethical, and Global Implementation Challenges

For multi-omics and AI-based approaches to transition from research to clinical applications, they need to be clinically validated, along with regulatory mechanisms that delineate the requirements for safety, analytic validity, clinical validity, and accountability. The large genomic, molecular, and clinical databases also raise issues of data privacy, consent, ownership, and sharing (Wan et al., 2022).

Cost and infrastructure-related challenges may be critical barriers in LMICs that carry the highest burden of TB. Many high-burden countries may not have the capacity to access high-end sequencing, computing resources, specialized labs, and trained personnel. Unless these challenges are adequately addressed, there is a risk of precision medicine being confined to high-resource settings and resulting in increased health inequity (Baba & Atinga).

9. Conclusion

TB is a highly heterogeneous disease, with clinical outcomes resulting from complex interactions between M. tuberculosis, the immune system, host genetics, metabolic processes, and tissue microenvironment. Although population-based approaches have been critical in TB prevention and control, they do not fully account for the large inter-individual differences in TB disease course and treatment outcome.

Multi-omics techniques, such as combining genomics, transcriptomics, proteomics, and metabolomics, offer a more holistic picture of TB disease, while single-cell and spatial methods provide insights into host responses at the single-cell level and in different tissue compartments. AI can help integrate and interpret such data to identify biomarkers, stratify risk, predict clinically relevant outcomes, and guide clinical decisions. Together, these technologies provide the basis for precision TB to facilitate more individualized TB diagnosis, prognosis, treatment, and surveillance. They may also help to drive the development of host-directed therapies and novel therapies.

However, implementing these approaches in clinical practice will require robust validation, standardization, transparent and trustworthy AI models, and scalable and affordable tools. In addition to further scientific and technological advances, equitable implementation is essential to ensure that precision TB can contribute to controlling the TB epidemic globally, especially in high-burden low-resource settings.

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