Disease Prevention and Epidemiology

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Review

Machine Learning in Tuberculosis: Advancements in Diagnostics, Drug Resistance Prediction, and Prognosis

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Abstract

Tuberculosis (TB) continues to challenge global health and has become much worse due to the complexities associated with diagnosis, the need to perform time-consuming culture-based drug susceptibility testing, and the emergence of drug-resistant strains. The integration of machine learning (ML) and Artificial Intelligence (AI) has transformed how we computationally approach TB control, providing approaches to use ML and AI as tools to assist with the entire scope of the disease, rapidly and accurately, without the need for invasive methods. This review highlights the recent developments in the application of ML models and highlights their potential use as diagnostic biomarkers (e.g., using host-gene-expression, metabolomics, and spectrographic data), predicting drug resistance from genomic sequencing (Whole-Genome Sequencing), and predicting patient prognosis and treatment outcome. Although there are many different algorithms that can produce predictive results, further work in developing capabilities for model interpretation and performing external validation using diverse cohorts from around the world is needed to enable the use of these novel tools to be incorporated into everyday clinical use; thereby supporting continued efforts to achieve global eradication of TB.

Keywords

Tuberculosis, Machine learning, Artificial intelligence, Biomarkers, Drug resistance, Whole-genome sequencing, Radiomics, Prognosis

Article History

Received: 02 December 2025
Revised: 26 January 2026
Accepted: 11 February 2026
Available Online: 24 February 2026

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (Mtb) that ranks among the three leading causes of death worldwide (after COVID-19 and HIV/AIDS) [1,2]. The continuing existence and severity of TB demand immediate and renewed global efforts to control TB spread. There are four pillars that will ultimately form the basis of effective TB control: rapid and accurate diagnosis, prompt identification of drug-resistant TB (DR-TB), strong clinical prediction of treatment response, and focused strategies for prevention [3].

Traditional methods of achieving these goals for TB have become increasingly insufficient in light of the present-day epidemiological needs for TB. Traditional diagnostic methods such as sputum smear microscopy, sputum cultures, and phenotypic drug susceptibility testing (DST) of Mtb strains are very labor-intensive and time-consuming to perform and have extremely limited sensitivity in cases of paucibaciliary TB (extrapulmonary TB or TB in children) [4,5]. For example, it can take 40 days for the results from a sputum culture to determine whether an individual is resistant to any specific antibiotic, resulting in delays in effective therapy for the individual as well as opportunities for increased transmission and amplification of antimicrobial resistance (AMR) [6,7].

The rapid growth of high-throughput capabilities has led to an increase in the development and availability of large-scale and/or complex types of Biological, Clinical and Genomic data which present many opportunities to utilize machine learning (ML) within TB management. The advantages of ML tools for processing large amounts of TB data and detecting patterns that traditional statistical methods and clinical rules cannot easily identify will likely allow for the development of faster, more accurate, and less invasive clinical decision support tools for TB [8-10]. By adopting ML methods, researchers will benefit from the advancement of key elements in the ML Paradigm Shift. The ability to aggregate these large, complex data sets into predictive Clinical Intelligence to facilitate Global TB Eradication is more achievable than ever before; thus, changing the way we utilize ML for TB research.

This comprehensive review summarizes the most recent use of ML and AI in the field of TB research from 2016-2025, with a focus on several major applications; Diagnosis and Differentiation, the prediction of drug resistance (DR), and the use of ML to predict prognosis and to generate epidemiological information about TB. The studies included in this article demonstrate a significant increase in the sophistication of ML tools being utilized over the years reflected in the increased use of increasingly advanced ML algorithms (RF, support vector machine (SVM), extreme gradient boosting (XGBoost), deep neural network (DNN), etc.) to perform analyses.

2. ML in Diagnosis and Differentiation

One of the most immediate and profound clinical impacts of ML is its capacity to drastically improve diagnostic speed and accuracy. This is particularly crucial in complex scenarios such as differentiating active disease from latent infection (LTBI), distinguishing TB from non-tuberculous mycobacteria (NTM) infections, or resolving diagnostic dilemmas like intestinal TB (ITB) versus Crohn's disease (CD) [11] (Figure 1).

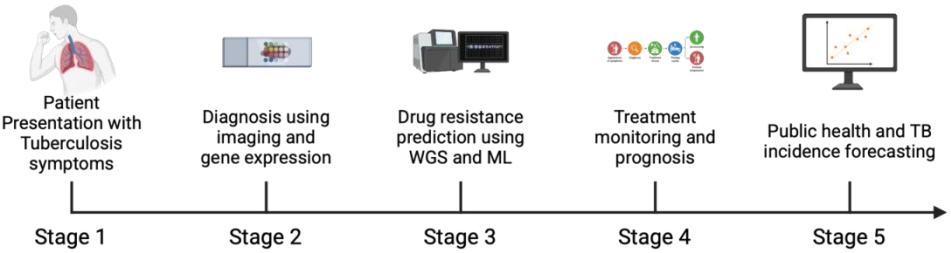

Figure 1. Clinical timeline of ML in TB. This figure summarizes the integration of ML approaches across the TB care continuum, from diagnosis to prognosis and epidemiological surveillance. It highlights how ML tools can support decision-making at multiple clinical stages rather than functioning as isolated solutions. The timeline contextualizes the evolving role of ML within real-world TB management pathways.

2.1 Leveraging Biomarker Signatures with ML

ML models are revolutionizing the identification of new diagnostic signatures derived from host immunological response (transcriptomics, proteomics) and metabolic profiles (metabolomics).

The evolution of Mtb infection activates multiple intricate and changing ways in which the host's immune system will respond to Mtb infection; these responses leave a series of fine transcriptomic and proteomic marks on the body. While many aspects of these patterns are too complicated for typical analytical procedures to fully appreciate, ML methods have been extremely good at using ML algorithms to unlock complex or multidimensional data to develop tools for the improved identification and characterisation of patients with TB (Figure 2). There have been successful attempts to produce classifiers derived from host-gene-expression patterns for diagnosing active TB (ATB). An international cooperative effort led to the design of the TB-Scope ensemble ML model using a host-gene-expression pattern; this model built off 143 feature genes identified from data sets of 1258 samples using microarray techniques and provided

reliable performance in its ability to diagnose ATB via a total of twelve independent validating datasets, including RNA-seq data from 1786 samples, that collectively suggested that it has very strong generalisability on diverse platforms and in multiple global cohorts [12]. Additionally, a combination of blood transcriptome analyses led to an identification of ten numbers of genes (the initial 10-gene signature), which had excellent predictive accuracy (as evidenced by the area under curve (AUC) in receiver operator characteristic (ROC) and precision-recall) in successfully distinguishing ATB patients from controls and identifying potential patients at risk for developing the active form of TB [13].

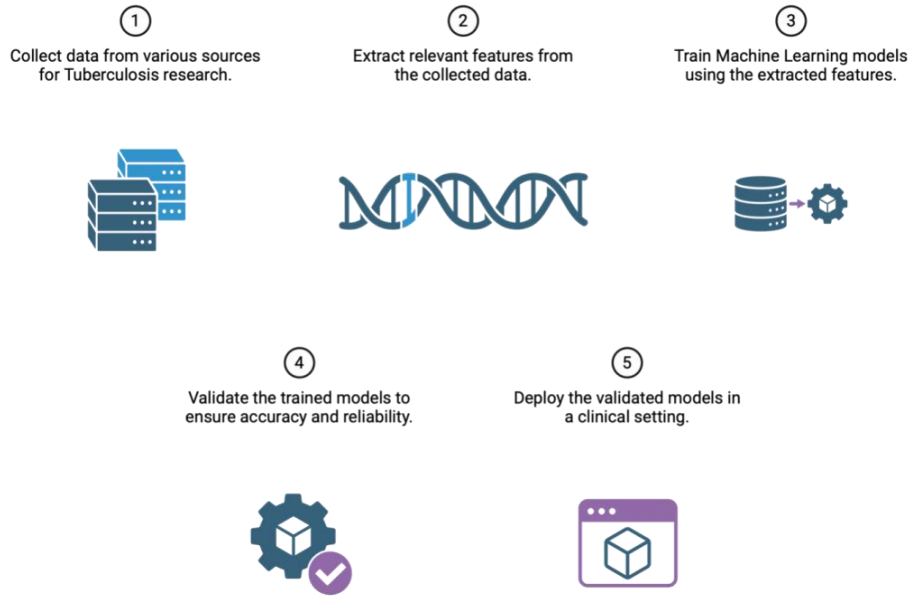

Figure 2. ML pipeline protocol for TB diagnosis. This figure illustrates the general ML workflow applied to TB diagnosis, including data acquisition, feature extraction, model training, and validation. It provides a conceptual overview of how heterogeneous biological and clinical data are transformed into predictive outputs. The schematic helps readers understand the methodological steps underlying reported diagnostic performance.

2.1.1 Differentiation of ATB from LTBI

The continuum between ATB and latent tuberculosis infection (LTBI) presents a significant challenge to diagnostic testing in that it requires a large number of variables to be successfully quantified. Therefore, a number of researchers have developed ML models so that the immunological markers can be used to better identify or indicate whether an individual has ATB or LTBI, thus creating a more precise discriminative ability for TB. For example, one such study combined results from the T-SPOT test (which measures the number of T cells in response to two TB-specific antigens [ESAT-6 and CFP-10]) with more complex traits of adaptive immunity (CD4 and CD8 T cells producing γ-interferon), and then used the cforest algorithm (conditional random forests (cforest)) as a classification model for the combined features. The cforest model had significantly higher discriminative power than any other models evaluated, with an AUC of 0.978 and sensitivity of 93.39% and specificity of 91.18% for the discovery cohort. Similar results were also achieved in the independent validation cohort [14]. Another model applied the gradient boosting machine (GBM) algorithm, which used common laboratory indicators (e.g., lymphocyte counts, albumin, etc.) to distinguish ATB from LTBI, and achieved good performances, with sensitivities of 87.63% and specificities of 91.34% in an independent validation cohort [15].

2.1.2 Immune-Cel-Associated Signatures

By using ML, scientists can identify immune-cell-related gene signatures, focusing specifically on genes linked to neutrophil extracellular trap (NETs), such as CD274, IRF1, and HPSE. These hub genes were established through the use of algorithms (SVM-RFE, least absolute shrinkage and selection operator (LASSO), and random forest(RF)) that predicted high accuracy (AUC 0.865-0.98; sensitivity/specificity >80%) in discriminating ATB from LTBI [16,17]. A monocyte-associated gene (MSRB2, CLEC4D, and ASGR2) has been identified as possible TB biomarkers based on ML and Mendelian randomization data and demonstrated strong accuracy when incorporated into a diagnostic model utilizing monocytes. This leads to suggested evidence of a possible causal association between increased TB risk and the use of CLEC4D [18].

2.1.3 Proteomics and Diagnostics

Using signatures of plasma proteins appears to provide a rapid method of diagnosing disease. A study demonstrated that a set of nine plasma proteins (CXCL9, PDL1, CDCP1, and IFNγ) produced an area under the receiver operating characteristic curve (AUC) value of between 0.89 and 0.99 in distinguishing patients with TB diseases from controls

[19]. Additionally, in adolescents and young adults, serum proteomics studies found three important biomarkers that had the highest accuracy and sensitivity for identification of ATB when ranked by SVM-RFE methodology; these included: the apolipoprotein A-I (APOA1) protein, beta-hemoglobin protein (HBB), and alpha-hemoglobin subunit-1 (HBA1) [20].

2.1.4 Metabolomic and Other Omics Signatures

Metabolomics provides insights on how the host interacts with a pathogen, based on the chemical composition of the organism. When looking at plasma metabolomic profiles for TB patients, ML analysis has revealed a significant increase in both fat and protein metabolite levels in patients with both smear-positive pulmonary TB (SPPT) and smear-negative pulmonary TB (SNPT). Using ML with the multilayer perceptron (MLP) model, a model that uses 10 input features that includes lipid/lipid-like molecules and organic acid/derivatives, the authors showed excellent predictive capability for the simultaneous classification of SPPT, SNPT, and control groups (94.74% correct) [21]. For differentiated active TB from those without TB (that's the difference between TB and those that do have NTM and LATBI), multi-omics analysis provided evidence for the lipid molecule PC(14:0_22:6) as the most significant metabolic marker; this marker was observed to consistently demonstrate lower concentrations in active TB patients and demonstrated areas under the ROC curve (AUCs) ranging from 0.77-1.00 for validation sets, indicating it is an excellent potential marker for active TB diagnosis [22]. To find markers of lymphnode TB (LNTB), researchers used untargeted metabolomic profiling in conjunction with both SVM and RF ML models, with caretaker markers identified Leu-Ala at AUC 0.8292; a marker indicating dysregulation in the biosynthesis of phenylalanine, tyrosine and tryptophan, may be a key feature of LNTB [23].

2.2 Advanced Rapid and Non-Invasive Diagnostic Platforms

The long turnaround time of conventional testing necessitates the development of rapid, non-invasive diagnostic platforms suitable for point-of-care (POC) settings, greatly enhanced by ML.

2.2.1 Spectroscopy-Based Diagnosis

Raman spectrometry (RS) and surface-enhanced raman spectrometry (SERS) have been employed for rapid, non-invasively detecting TB from sputum (spit) and/or serum (blood) samples. Using the principal component analysis (PCA) with SVM models to compare the spectral differences of biomolecules (lactate, beeta-carotenes, amide I), an overall diagnostic accuracy of 92% with high specificity (98%) was obtained [24]. A hand-held RS device and deep-learning algorithms were also able to distinguish between sputum samples containing Mtb and those without, achieving 94.32% accuracy based on five-fold cross-validation, and accurately profiled drug-resistant strains, achieving 99.59% accuracy, providing a pathway for rapid POC diagnosis [25]. SERS sensors were used for LTBI (latent TB infection) screening by analysing the plasma samples from patients. Using logistic regression, the model was found to have good accuracy levels (93%) due to optimisation of both sample collection and data processing pipelines, suggesting the potential use of this technique as a tool for LTBIs screening [26]. Fourier transformer infrared spectrometry (FTIR) combined with an XGBoost classifier yielded the highest overall AUC score of 0.82 for the rapid screening of TB patients' plasma compared to both Logistic Regression and RF classifiers, using protein and lipid spectral difference information [27].

2.2.2 Electronic and Exhaled Breath Sensing

Detection of volatile organic compounds (VOC) in the breath of patients can provide a new method for diagnosis that doesn't require invasive procedures. For example, an electrochemical sensor with an XGBoost algorithm that detects methyl-nicotinate (a VOC) has been developed as a potential biomarker for active pulmonary TB. In a clinical trial of the sensor, it was found that the XGBoost algorithm could accurately classify TB status with an accuracy of 78% (Sensitivity=71%, Specificity=100%) based on the gathered data [28]. Another example of using breath analysis is demonstrated by a study which analyzed exhaled breath samples collected through multidimensional gas chromatography time-of-flight mass spectrometry (GC-TOF MS) along with a RF approach to determine a panel of 46 different features to distinguish pulmonary Mtb infection from other disease processes [29]. In addition to using breath analysis, the use of nanomotion technology provides a novel growth-independent method for determining antibiotic susceptibility. Through measuring bacterial vibrations, this technology has been combined with artificial intelligence (ML techniques) to predict strain phenotype for isoniazid and rifampicin with 100% sensitivity and 100% specificity using the combined recordings from this technology. This innovative combination of nanomotion technology and Artificial Intelligence has reduced the time to obtain results from weeks to only 21 hours [30].

2.3 Multimodal Differentiation and Imaging (Radiomics)

ML models are adept at resolving complex diagnostic dilemmas that rely on multimodal clinical, laboratory, and imaging data (Table 1).

Table 1. ML in TB diagnosis and differentiation.

Diagnostic Task	ML Model	Data Type/Key Biomarkers	Performance (As reported)	Validation
Active TB diagnosis	Ensemble ML (TB-Scope)	Host gene expression (143 genes)	High diagnostic accuracy reported across multicenter cohorts	External, multicenter
ATB *vs.* LTBI	Conditional RF	T-SPOT, CD4/CD8 IFN-γ	High AUC, sensitivity and specificity reported	Internal+ external
ATB *vs.* LTBI	GBM	Routine laboratory indicators	Good sensitivity and specificity reported	External
ATB vs non-TB	Multi-omics ML	Lipid PC(14:0_22:6)	Strong discriminative performance reported	Internal
Smear±PTB *vs.* control	MLP	Metabolomics	High classification accuracy reported	Internal
ITB *vs.* CD	XGBoost	Clinical+T-SPOT features	High AUC reported	Internal
Spinal TB *vs.* pyogenic	Multimodal ML	PNR, NLR, HGB	Good diagnostic performance reported	Internal
Rapid POC TB	SVM+Raman	Serum biomolecules	High accuracy and specificity reported	Internal
NTM-PD *vs.* PTB	SVM+CT radiomics	Radiomics features	High validation AUC reported	External

2.3.1 Pulmonary Disease Differentiation

CT radiomics features were collected and examined with many types of ML algorithms to create an analytical model that could help distinguish between NTM pulmonary disease and pulmonary tuberculosis (PTB) (Figure 3). The SVM model had superior performance, with a validation AUC of 0.87739, compared to RF and XGBoost models [31]. In a different multimodal ML process, a light gradient boosting model (LightGBM) algorithm was used in conjunction with clinical data (i.e., IL-6 levels, patient gender, and patient age), and CT image data to achieve an external testing accuracy of 74.5% when attempting to differentiate NTM from Mtb. This method performed better than the current radiologists' assessment and previous ML programs [11]. When differentiating between lung adenocarcinoma and TB lesions ML-based radiomics models significantly outperformed clinical models, achieving an AUC of > 0.94. The predictive capacity of ML-based radiomics models remained consistent regardless of whether the cavity was included in the Region Of Interest; the performance was not affected regardless of whether the cavity was included or excluded [32]. In the abdominal cavity, a model that included clinical characteristics and primary CT signs such as omental rim signs, peritoneal nodules, and large quantities of ascites was able to accurately distinguish between peritoneal tuberculosis and peritoneal carcinomatosis (PC), achieving an AUC of 0.971 in training and 0.914 in test data [33].

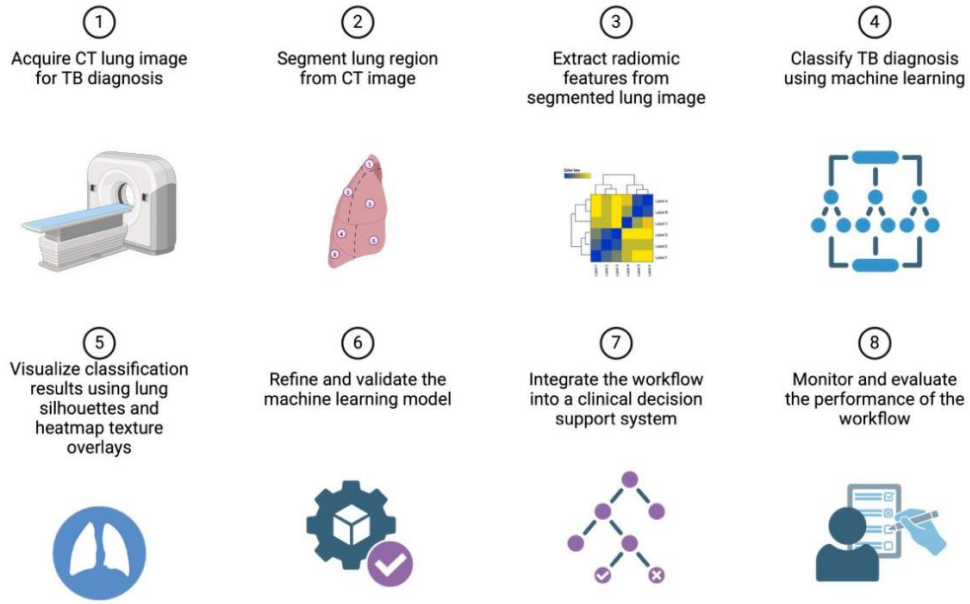

Figure 3. TB imaging radiomics workflow. This figure depicts the radiomics-based workflow for TB imaging analysis, from image acquisition and segmentation to feature extraction and model prediction. It demonstrates how complex imaging patterns can be quantified and integrated with ML classifiers to improve diagnostic differentiation. The figure emphasizes the importance of standardized imaging pipelines for reproducible radiomics-based models.

2.3.2 Gastrointestinal and Spinal Differentiation

The distinction between CD and ITB is paramount for effective therapy. Collectively, studies report that the use of XGBoost (such as with T-spot test results, pulmonary TB history, and age of onset) outperformed other algorithms, AUC of 0.946 and an accuracy of 0.884 [34,35]. In addition, a much more advanced multidisciplinary approach was taken by integrating deep-learning radiomic features from MRI, CT scan images, clinical evaluations, along with multilayered pathology evaluation to arrive at a higher-quality AUC of 0.94 [36]. In spinal diseases, machine-learning algorithms have also been developed to distinguish spinal tuberculous and pyogenic spondylitis patients using four machine-learning algorithms to identify seven significant blood parameters, including platelet neutrophils ratios (PNR), neutrophils to lymphocytes ratios (NLR) and hemoglobin (HGB), to build a nomogram to diagnose patients and generate an AUC of approximately 0.83 for validated testing [37]. Lastly, ML is being applied to help predict future problems, including in spinal cord injury in tuberculous patients, where the RF method was deemed the best predictor (with an AUC for the testing set of 0.816), with Monocyte counts identified as the primary indicator [38].

In the context of TB diagnosis, an AUC approaching 0.90 indicates strong discriminative ability between disease states; however, clinical utility depends on the balance between false-positive and false-negative results. In high-burden settings, false negatives may delay treatment and facilitate transmission, whereas false positives can lead to unnecessary therapy and toxicity. Therefore, ML-based diagnostic tools must be evaluated not only on AUC but also on sensitivity thresholds aligned with World Health Organization (WHO) target product profiles, particularly for screening and triage applications in resource-limited environments.

Across diagnostic applications, model performance is strongly influenced by data modality and feature structure. Tree-based ensemble methods such as RF, Gradient Boosting, and XGBoost consistently outperform linear models when applied to structured clinical, laboratory, and immunological datasets, owing to their ability to model non-linear interactions and handle feature heterogeneity. In contrast, deep learning approaches, including convolutional neural networks (CNN), demonstrate superior performance in high-dimensional data contexts such as imaging, spectroscopy, and transcriptomics, where hierarchical feature extraction is critical. However, several studies highlight that simpler models may outperform deep learning in scenarios involving limited sample sizes, sparse biomarkers, or strong signal-to-noise ratios, reducing overfitting risk. Importantly, while deep learning models often achieve higher AUCs, their limited interpretability poses challenges for clinical adoption, reinforcing the value of interpretable ensemble models in POC and low-resource diagnostic settings.

3. ML in DR Prediction and Anti-TB Drug Discovery

The rapid emergence of DR-TB, including multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains, necessitates tools that can quickly and accurately predict resistance profiles to inform treatment. ML models, particularly when paired with whole-genome sequencing (WGS) data, have become the gold standard for genotypic resistance prediction [39,40].

3.1 Genomic-Based Resistance Prediction

ML models consistently demonstrate superior performance over conventional rules-based algorithms by capturing the complex mechanisms of resistance, including rare variants, gene-gene interactions (epistasis), and non-canonical mutations [41,42].

3.1.1 Model Comparison and Performance Metrics

Significant research into the predictive power of tree-based ensemble algorithms, particularly gradient tree boosting (GTB) and RF, using extensive WGS datasets generated from 35,777 isolates from many countries worldwide, such as the CRyPTIC dataset, revealed that these tree-based methods could effectively predict resistance to both first-line and second-line drugs (AUC values for first-line, 0.883-0.965). Across 14 anti-TB drugs, the RF models demonstrated high predictive performance for the majority of the drugs that surpassed AUC values of 96% for 4 first-line drugs, which included amikacin, kanamycin, ciprofloxacin, moxifloxacin. Even busy developing disruptive technologies, many researchers have been exploring ML modelling platforms using (ANN) (e.g., CNN) to develop predictors of AMR based on WGS sequencing data from patient isolates. The analysis compared LR, RF and 1D CNN models developed using 10,575 isolates and found that 1D CNN produced the best results and produced stable classifiers with F1 scores ranging from 93.7% (rifampicin) to 97.2% (ofloxacin) and consistently stable results across various drugs compared to the other two techniques. The gradient boosting classifier (GBC) has also shown to be among the highest performers; the GBC achieved correctly identified percentages of 97.28% for rifampicin and 96.06% for isoniazid, thus supporting the premise that boosting methods are highly robust [43,44].

Using ML techniques to evaluate the efficacy of the drugs used for treating TB has provided significant improvements over the traditional methodologies. Specifically, the use of ML provides a 2%-4% increase in the sensitivity of several first-line TB therapies–isoniazid, rifampicin and ethambutol–compared to standard rule based analyses. The maximum sensitivity achieved was 97% for these three agents. The most significant increases were observed for the

fluoroquinolone antibiotics (ciprofloxacin is used to treat DR-TB), which achieved a sensitivity of 96% for DR-TB. There were increases of 12% for moxifloxacin and 15% for ofloxacin, achieving a sensitivity of 95% and 96% respectively compared with standard methods. In addition, the ML approach improved the sensitivity of pyrazinamide and streptomycin, increasing the sensitivity by 15% (84% with pyrazinamide) and 24% (87% with streptomycin), respectively [45,46].

3.1.2 Identifying Novel Resistance Markers and Mechanisms

The use of advanced methods for statistical learning-specifically developed to capture the full range of both common and uncommon (rare) sequence variants within the human genome–has improved the predictive accuracy. On first-line drugs, it increased the sum of specificity and sensitivity by 11.70% as compared with models that use only canonical mutations. On second-line drugs, the increase was 3.20% [47]. The difficulty associated with conducting phenotypic PZA testing creates strong need for models like the one created in this study. The available ML models, through the development of an explainable model using an explainer ML framework and performance data from an explainable CNN model that produced a 93% accuracy measure, also demonstrate the advantage of having an SVM model that produces the same feature identification as the explainer ML. The results of SVM also confirm the earlier findings and demonstrate two additional resistance-related genes (embB and gyrA) not previously described in the literature as well as supporting continued molecular study of the pncA gene for greater understanding of guinea pig-to-human transmission [48]. The results from the study using a gradient-boosted decision tree for PZA prediction based on chemical features and structure of PZA protein achieved 80.20% sensitivity and 76.90% specificity on a hold-out dataset used for validation purposes [49]. Additionally, the prediction of rifampicin resistance can be done using ML methods employing the rpoB gene, with ensemble decision tree models yielding moderate accuracy–within also Todd's [50]. The use of eXplainable Artificial Intelligence (XAI) or Explainable AI techniques with SHAP demonstrated the ability to support both performance evaluation of known resistance mutations, consistent with the WHO catalogue, as well as to predict more than one hundred new resistance mutations for 13 antibiotics located in genes beyond those traditionally associated with RIF resistance, demonstrating the ability of ML to drive novel mechanism discovery [51]. The output of genomic ML models is increasingly being translated into actionable clinical tools. For example, GenTB is a free and open web-based application utilizing RF and a wide and deep neural network to rapidly and accurately predict resistance profiles to multiple anti-TB drugs. GenTB's mean sensitivities were marginally higher than leading existing tools, demonstrating its utility in guiding individualized treatment regimens based on WGS data [52].

3.2 ML in Anti-TB Drug Discovery and Repurposing

ML is significantly accelerating the typically slow and resource-intensive pipeline for new anti-TB drugs by enabling high-throughput virtual screening (HTVS) and property prediction (Figure 4).

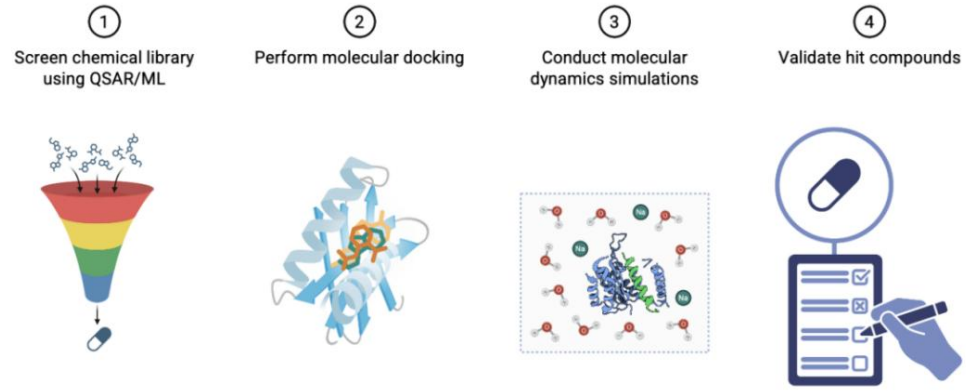

Figure 4. Drug Discovery Pipeline with ML for TB. This figure outlines the application of ML within the anti-TB drug discovery pipeline, including virtual screening, target identification, and candidate prioritization. It highlights how ML accelerates early-stage drug discovery by reducing experimental search space. The diagram also underscores the need for downstream biological validation of computationally identified candidates.

Virtual Screening and Target Identification: ML techniques such as SVM, K-Nearest Neighbors (KNN), RF, and Gaussian Naive Bayes (GNB) are excellent tools for virtual screening to classify active or inactive compounds against target(s) of pathogenic Mtb [53]. A virtual screening process employing various ML and Deep Learning (DL) algorithms has been successfully used to identify, validate and evaluate two promising drug repurposing candidates, namely aldoxorubicin and quarfloxin, that exhibit potent inhibition of the Mtb H37Rv strain as well as effectiveness against drug-resistant isolates . Molecular dynamics (MD) simulations were conducted to confirm the ability of these two agents to bind to the Mtb DNA gyrase [54]. In addition, computational drug repurposing strategies utilizing ML have been used to successfully discover novel dual-targeted inhibitory compounds against the aminoacylation of tRNA for the mycobacterial enzymes Leucyl-tRNA Synthetase (LeuRS) and Methionyl-tRNA Synthetase (MetRS) [55].

Further investigations revealed the identification of other novel inhibitors of Mtb Topoisomerase I through the virtual screening of ML algorithms [56,57]. ML techniques have also been implemented to identify potential inhibitors of Pantothenate Synthetase [58] and Thymidylate Kinase for Mtb, and a combination of RF, XGBoost and Deep Neural Network (DNN) models achieved the highest accuracy indicator (AUC: 0.942 on the external testing dataset) for predicting active compounds [59,60]. The molecular targets prioritized by ML-based drug discovery approaches are biologically compelling due to their essential roles in Mycobacterium TB survival and replication. Enzymes such as leucyl-tRNA synthetase (LeuRS) and methionyl-tRNA synthetase (MetRS) are critical for protein synthesis, while DNA gyrase and topoisomerase I are indispensable for DNA replication and transcription, making them attractive targets for bactericidal activity. However, despite strong in silico performance, ML-based predictions remain limited in their ability to account for mycobacterial cell-wall permeability, intracellular drug accumulation, and host-pathogen interactions. Consequently, many computationally identified hits fail to translate into in vivo efficacy. Integrating ML predictions with experimental validation, pharmacokinetic profiling, and systems-level biological insights is therefore essential to bridge the translational gap between virtual screening and clinically effective anti-TB therapies.

In DR prediction, ensemble tree-based models and deep neural networks applied to WGS data consistently outperform traditional rules-based approaches by capturing rare variants, epistatic interactions, and non-canonical resistance mechanisms. Gradient boosting and RF models provide a favorable balance between predictive performance and interpretability, particularly when combined with explainability frameworks such as SHAP. Deep learning architectures, including 1D CNNs, achieve the highest predictive accuracy in large-scale genomic datasets but require extensive training data and careful validation to avoid overfitting. In drug discovery, ML-enabled virtual screening significantly accelerates hit identification; however, predictive performance remains constrained by biological complexities such as mycobacterial cell-wall permeability and intracellular drug activity. These findings underscore the need for biologically informed ML pipelines and external validation to bridge the translational gap between in silico predictions and experimental efficacy.

4. ML in Prognosis and Epidemiology

The utility of ML extends beyond diagnosis and resistance, proving instrumental in predicting disease progression, treatment failure, adverse events, and public health trends, thus strengthening patient management and control strategies (Table 2).

Table 2. ML in TB DR and prognosis.

Prediction Task	ML Model	Data Type	Performance (as reported)	Validation	Reference(s)
WGS Drug Resistance (multi-drug)	1D CNN	SNPs, pan-genome	F1-scores 93.7-97.2%	External	[44]
PZA resistance	Deep CNN (Explainable ML)	WGS	~93% prediction accuracy	Internal	[48]
MDR/RR-TB outcome	ANN	Clinical+SCC	High prognostic accuracy (AUC ~0.90 for SCC prediction)	Internal	[61-63]
LTFU (pre-treatment)	LightGBM	National registry data	AUC 0.71-0.72	External	[64,65]
LTFU (clinical setting)	XGBoost	Clinical+social factors	AUC 0.921	Internal	[66]
MDR-TB non-compliance	Logistic regression-based ML	Clinical+behavioral factors	AUC 0.79	Internal	[67]
ATB-drug-induced liver injury (DILI)	ANN	Clinical+NAT2 genotype	Accuracy 88.67%, AUC 0.898	Internal	[68]
ATB-DILI (interpretable model)	XGBoost+SHAP	Clinical+liver markers	Improved over RF/LASSO; SHAP-identified predictors	Internal	[69]
Pediatric DILI	GBM (AutoML)	Drug exposure, BMI	AUC 0.784	Internal	[70]
Pulmonary embolism in TB	RF	Clinical+sociodemographic	AUC 0.839	Internal	[71]
Active TB prediction in HIV	RF	Clinical data	AUC 0.83	Internal	[72]

4.1 Predicting Treatment Outcomes and Patient Management

Identifying individuals who have the potential to be unsuccessful with treatment is important for the development of ethical targeted early clinical intervention for patients with diseases that require extended therapy with chemotherapy (e.g., cancer) (Figure 5). ML has been found to be particularly useful in predicting patient outcome for treatment, with ML prediction models producing an improvement in estimated accuracy greater than 12% compared to baseline. As a

result, predictive capability will also give individuals a higher priority in being supported through more intensive and focused methods by health workers, making overall program efficiencies higher.[61] Predicting treatment outcomes such as sputum culture conversion (SCC) will allow better management of patients with rifampin-resistant TB, as it is important for predicting the best possible outcome for the disease [62]. An ANN model exhibited superior generalizability and stability than a logistic regression model in predicting SCC, with a 6-month AUC of 0.90, which is an excellent tool for rapidly assessing the potential therapeutic benefit of therapy [63]. A RF model that focused on SCC failed to include other potential predictors of outcome such as levofloxacin resistance. But the top predictors of SCC failure were embB_p.Met306Ile and smear positivity at two months post-therapy initiation and highlight the involvement of genomic and clinical factors in determining failed treatment.

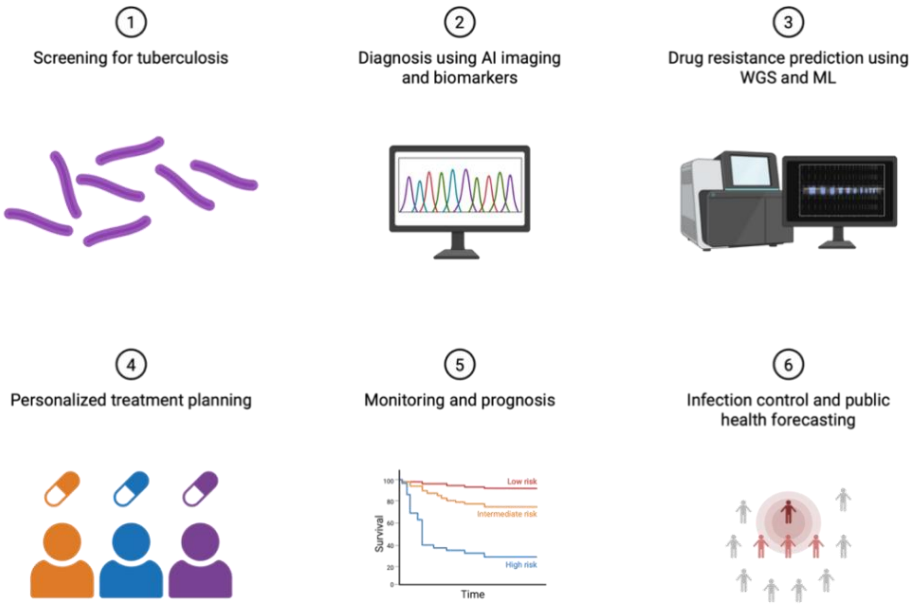

Figure 5. TB Patient Journey. This figure maps the patient journey across TB diagnosis, treatment, and follow-up, indicating stages where ML can support clinical decision-making. It illustrates how predictive models can assist in risk stratification, adherence monitoring, and outcome prediction. The figure reinforces the potential of ML to enhance patient-centered TB care.

Loss to Follow-up (LTFU) and Non-adherence: The identification of the predictors of LTFU is an important area of focus in public health, particularly regarding the prevention of MDR-TB. Models based on large national registries (such as the Brazilian Reporting System for Notifiable Diseases-SINAN) are available to help predict LTFU risk based on easily accessible variables including prior TB history and treatment, substance abuse, age, gender, HIV status and educational achievement during the TB treatment process. The LightGBM performed consistently better than other methods (receiving an area under curve (AUC) score between 0.71 and 0.72) in internal and external validations and provides for the potential to direct resources towards patients likely to discontinue treatment before the start of treatment [64,65]. In the clinical environment, the XGBoost algorithm was the top-performing method (overall AUC of 0.921 for predicting pre-treatment LTFU compared to the SVM and RF algorithms, with the most important predictive variables being education level, prior history of hospitalizations, history of alcohol consumption and prior history of TB treatment [66]. Using data from the admission tests taken by patients, ML models can predict clinical indicators for discontinuation of treatment and related to patient clinical and laboratory studies. A KNN classification approach that makes use of admission test results demonstrated an AUC of 0.87, identifying increased levels of 5′-nucleotidase, uric acid and globulin as the most successful early warning indicators for potential treatment failure [2]. For MDR-TB patients, a logistic regression-based ML algorithm identified educational status, registration group, treatment support, model of care, and khat use as significant prognostic features for treatment non-compliance (AUC 0.79) in a follow-up study cohort [67].

4.2 Predicting Adverse Drug Reactions, Co-infection, and Complications

ML is critical for managing patient safety and complex co-morbidities.

4.2.1 ATB-DILI

Knowing patients' risk of DILI is very important for ensuring safe treatment with prolonged courses of chemotherapy. In earlier studies comparing various ML methods, the ANN model that used both clinical (e.g., age/sex) and genomic factors (e.g., NAT2 genotype) showed the highest accuracy (88.67%) and AUCs (0.898) in predicting DILI, compared to SVM and RF [68]. Recently, interpretable models, such as XGBoost with SHAP analyses, have been used for DILI prediction, producing better results than RF and LASSO methods. The SHAP analysis showed the importance of baseline liver-related conditions (DILI, DIH, and fatty liver disease), age, and baseline liver enzyme levels (ALT, Tbil) in predicting a patient's DILI status [69]. In children and adolescents, an AutoML model using a GBM model achieved

a higher predictive accuracy (AUC 0.784) than traditional models in predicting ATB-DILI risk. The TreeShap method identified the plasma peak concentration (Cmax) of rifampicin and body mass index (BMI) as key features for the forming of personalized medication regimens for this group of patients [70].

4.2.2 Co-infection and Complications

Using ML, the risk of developing pulmonary embolism among TB patients was able to be predicted based on an analysis of the clinical and sociodemographic data of those patients. Indeed, the RF model has been found to outperform other ML models, producing an AUC of 0.839 [71]. In addition, ML models have also been successfully utilized to predict the risk of developing incident abdominal tuberculosis among patients co-infected with HTLVI and HTLVII. RF models based on routine clinical data including WHO disease stage and cough <4 weeks identified patients at highest risk for developing ATB, and have produced an AUC of approximately 0.83 during training, demonstrating potential to outperform current diagnostic strategies (Tuberculin Skin Tests or Interferon-Gamma Release Assays) when identifying high-risk patients who would benefit from preventive therapy [72].

4.3 Epidemiology, Public Health Control, and Forecasting

ML models provide essential predictive intelligence for public health officials to forecast incidence, allocate resources, and manage outbreaks.

4.3.1 Incidence Forecasting

Predicting TB incidence relies heavily on time-series and ML models. A summary of predictive algorithms for predicting the rate of TB incidence lists ARIMA, SARIMA, ETS, GRNN, BPNN, NARNN, NNAR, and RNN as the most frequently used techniques [73]. In order to accurately forecast time-series data on TB incidence rates for Anhui Province, China using an ensemble method called 'fusion modelling', researchers created a new algorithm combining RF, Recursive Feature Elimination, LASSO and.Partial Swarm Optimisation to process multiple inputs. This model performed exceptionally well (test set R^2:0.8634) [74]. Using ML algorithms with socio-economic and environmental variables such as population density, per person GDP and concentration of PM10 pollution, researchers used ML to predict PTB incidence rates and determine which socio-environmental factors are the key predictors for predicting incidence rates of TB, and identified important risk thresholds for planning interventions [75]. In addition, using Average Daily Temperature, Number of Sunshine Hours and PM10 as features, the BP Neural Network was found to produce the most accurate forecast of TB incidence trends [76].

4.3.2 Bovine TB (bTB) Control and Predicting Cluster Growth

Animal health (i.e., disease monitoring and treatment) has been a major use of ML. In researching bovine Tuberculosis (bTB), researchers developed models using Classification Tree Analysis and RF to accurately identify herd-level breakdowns of bTB. These models produced AUCs above 80%. In addition, evidence suggested that the most common predictors of herd-risk for bTB breakdowns were the local prevalence of bTB in the 100 nearest herds; time since last confirmed breakdown; slaughterhouse destination; and distance to closest slaughterhouse. The information gained from these models allows for improved targeted control of bTB in geographic areas, such as the United Kingdom. The predictive power of the models also allows for increased sensitivity of the test-and-slaughter system by enabling faster detection of herds that may meet criteria for receiving the rack test. Finally, ML methods for predicting which existing Bovine TB Genotypic Clusters are at greatest risk for "unexpected" future growth, have been shown to exist. These models indicate the time interval between new cases of Milkers that have persistent or extended time intervals, represent a better measure of risk than individual cases of Bovine TB or Clusters [77,78]. Thus, ML models provide a public health framework for determining potential health priorities, and using efficient, targeted measures to manage or intervene in ongoing transmission of BTBs.

Prognostic and epidemiological ML models demonstrate strong utility in predicting treatment outcomes, LTFU, adverse drug reactions, and disease incidence trends, particularly when leveraging large registry-based datasets. Gradient boosting and RF models consistently outperform traditional regression approaches due to their robustness to missing data and complex feature interactions. Notably, models trained on national surveillance datasets exhibit greater generalizability compared to single-center clinical cohorts. However, limited external validation and geographic bias remain critical barriers to clinical translation. While high predictive performance is frequently reported, integration into routine care requires transparent calibration, explainability, and alignment with public health workflows, particularly in resource-limited, high-burden settings.

4.3.3 Methodological Challenges and Sources of Bias in ML-Based TB Studies

Despite promising performance metrics, several methodological challenges limit the generalizability and clinical translation of ML models in TB research. A major concern is class imbalance, particularly in tasks such as differentiating active tuberculosis from latent infection or predicting MDR-TB versus drug-sensitive TB, where minority classes are often underrepresented. This imbalance can lead to inflated performance metrics if not properly addressed through resampling strategies, class weighting, or appropriate evaluation metrics. Overfitting remains a

persistent issue, especially in studies using small, single-center datasets or high-dimensional omics data. Complex models, including deep neural networks, may capture dataset-specific noise rather than biologically meaningful patterns, resulting in reduced performance when applied to external cohorts. This risk is compounded by limited external or prospective validation in many studies.

Another important limitation is spectrum bias, arising from the frequent use of hospital-based or referral-center cohorts that may not reflect the clinical diversity encountered in community or primary-care settings. Models trained on such datasets may perform poorly in real-world screening or POC environments. Additionally, substantial geographic and demographic bias exists, with many models trained predominantly on data from high-income or single-country populations, despite the highest TB burden residing in low- and middle-income regions. Finally, data heterogeneity across omics platforms, imaging protocols, sequencing pipelines, and laboratory assays introduces variability that is often insufficiently addressed. Differences in sample processing, feature extraction, and annotation standards hinder reproducibility and cross-study comparison. Addressing these challenges through standardized reporting, multicenter data sharing, and rigorous external validation is essential for advancing ML-based TB tools toward clinical implementation.

5. External Validation and Clinical Translation Readiness of ML-Based TB Models

Although many ML models for TB report high predictive performance, external validation remains a major bottleneck for clinical translation. A substantial proportion of studies rely on internal cross-validation or single-center retrospective datasets, which limits confidence in real-world generalizability. Only a minority of diagnostic models—primarily those based on host transcriptomics or large radiomics datasets—have undergone multicenter or geographically diverse validation, while prospective evaluations in routine clinical workflows are rare.

Based on the level of validation and clinical integration, existing ML-based TB studies can be broadly categorized into three stages of translation readiness. Proof-of-concept models demonstrate technical feasibility but are trained and tested

6. Conclusion

By integrating ML into the various aspects of TB research, from creating new laboratory methods for drug development through clinical diagnostics to tracking disease outbreaks globally, we have seen a huge advancement in the fight against one of the most challenging diseases to treat. The development of ML models has allowed researchers to identify new, non-traditional biomarkers in complex biological fluids that would have gone unrecognised by conventional means (e.g. the lipid PC(14:0_22:6) or the protein signature of CXCL9/PDL1), which helps speed up the process of identifying new compounds that can be used to treat TB (e.g. aldoxorubicin and quarfloxin), as well as identifying highly reliable and accurate drug-resistance predictions based on WGS data, where traditional statistical and rule-based approaches have consistently performed poorly when compared with ML approaches. The use of advanced ensemble and boosted techniques such as the XGBoost and GBM algorithms has helped improve performance on many diagnostic (AUCs typically ≤ 0.90) and prognostic tasks.

The concurrent growth of emphasis on XAI through tools such as SHAP analysis will be vital for the transition of these models from laboratory to clinical settings. If we can explain the key predictive features of models, whether they be based on genomics (i.e., rpoB_p.Ser450), clinical parameters (e.g., BMI, Cmax of rifampicin), or environmental/spatial factors (i.e., PM10 concentration), we can create greater clinical trust in the model and foster adoption of these models into clinical practice. This is currently a critical hurdle for the field to overcome to achieve its global impact. We will need to build very large, globally diverse, and rigorously curated training datasets to support the generalizability of models, particularly across geographic regions, ethnic populations, and clinical settings (e.g., low-resource and high-resource clinical environments). Future research should place a high priority on rigorous external and prospective validation of current models, and on creating integrated multimodal platforms capable of combining genomics, radiomics, immunology, and clinical information for a more comprehensive assessment and management of the patient. By overcoming these translational challenges, ML will emerge as an invaluable tool for supporting the personalized treatment of patients, and for providing the evidence needed to meet the worldwide goal of eliminating TB.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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