Outcome Report for

Health Technology Assessment of using Whole Genome Sequencing for Tuberculosis in India

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Table of Contents

Abbreviations

ADR	Adverse drug reaction
ATD	Anti-tubercular drug
DST	Drug Susceptibility Testing
FL LPA	First-line Line probe assay
ICER	Incremental Cost Effectiveness Ratio
LC DST	Liquid culture Drug sensitivity test
MDR	Multidrug resistant
NAAT	Nucleic Acid Amplification Test
NTEP	National Tuberculosis Elimination Programme
QALY	Quality adjusted life years
SL LPA	Second-line Line probe assay
TB	Tuberculosis
UDST	Universal Drug susceptibility testing
WGS	Whole Genome Sequencing
XDR	Xtremely drug resistant

Introduction:

Globally, there were estimated 1.6 million deaths due to Tuberculosis (TB) in 2021. India accounts for 25% of the estimated deaths with highest burden of TB in the world (1). Prevalence of multidrug-resistant (MDR)-TB was found to be 2.5% among new patients and 16% among previously treated patients. There are 1.3 lac cases of MDR-TB/Rifampicin-resistance (RR) estimated annually, and 9.5% of MDR-TB cases are Xtremely drug resistant (XDR) TB (2).

Despite the longstanding availability of effective treatment regimens, tuberculosis (TB) remains a challenge in many resource-poor settings. Figure 1 presents the diagnosis and treatment algorithm of the tuberculosis in India. Effective treatment delivery in India is compromised by low-sensitivity diagnostics and an unregulated private TB treatment sector that often provides substandard care, resulting in low cure rates and potential selection for multidrug resistance (MDR), defined as strains of TB resistant to at least isoniazid and rifampicin, two first line anti-TB medications. Recent innovations in diagnostic technologies could improve care at increased costs.

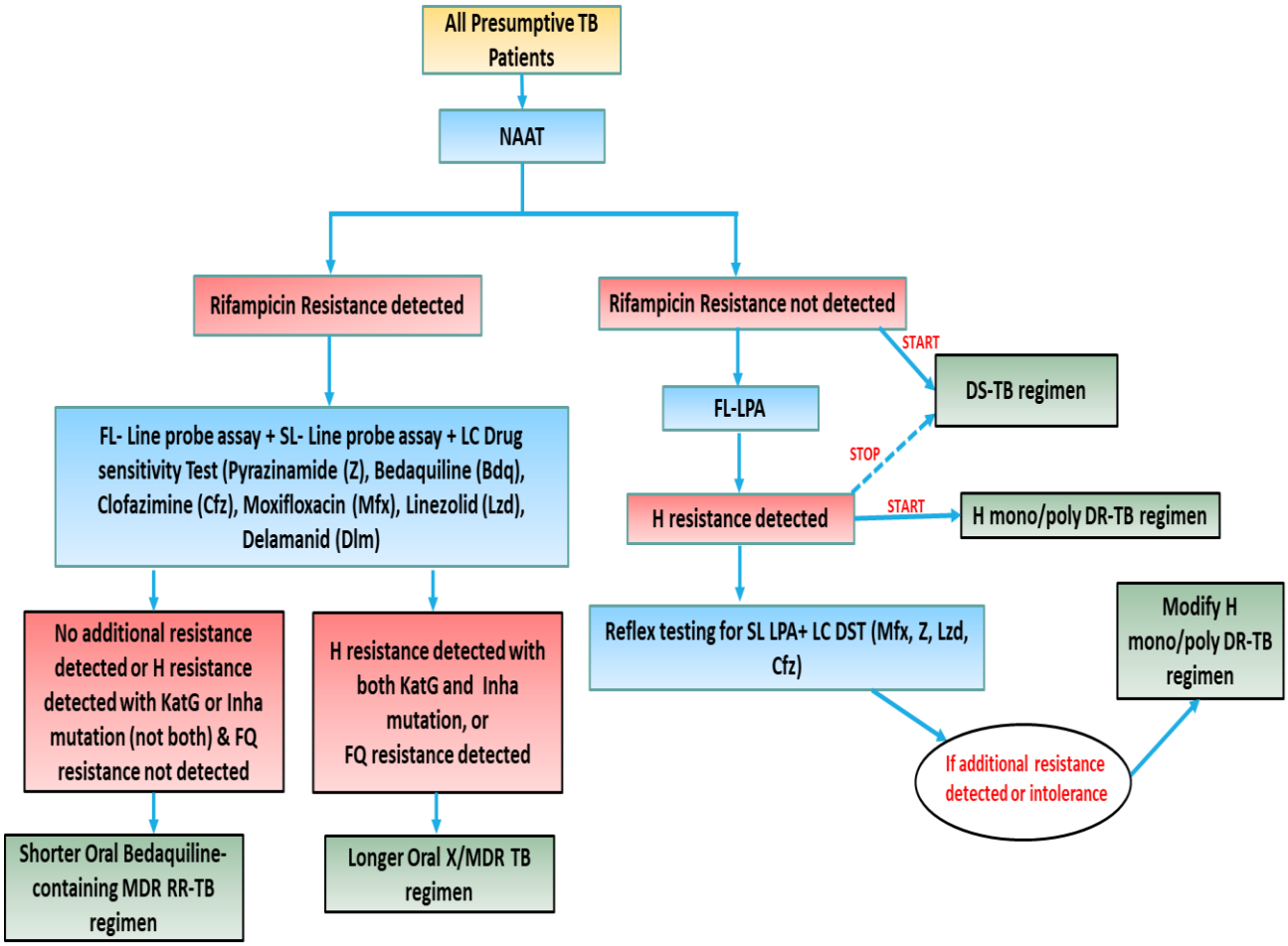
Drug-resistant tuberculosis (TB) has been a serious obstacle for global TB control programmes. TB patients with drug resistance may be induced by exposure to multidrug- and extensively drug-resistant tuberculosis (MDR/XDR-TB) strains or may develop as a result of other clinical factors, including delayed diagnosis, inappropriate treatment or poor compliance (3). Controlling the high prevalence of drug-resistant TB largely depends on a timely laboratory diagnosis. Traditional TB drug susceptibility testing (DST) relies on solid or liquid culture, which may take weeks or months to yield results. The slow growth of Mycobacterium tuberculosis is an impediment to the rapid diagnosis of anti-TB drug resistance, and aggravates the situation by increasing the incidence of MDR and XDR-TB in the world. Some rapid

molecular biology-based diagnostic methods have recently been applied in a clinical setting, including Xpert MTB/RIF and GenoType MTBDRplus (4-6). Although these methods are rapid and simple, their extension to undeveloped areas of the world is limited by prohibitive costs and availability. Low uptake of these technologies in Low- and Middle-income countries due to various reasons such as cost Limitations, need for specialized and well-trained staff, and lack of readily available data analysis and data storage solutions.

Whole-genome sequencing (WGS), as a molecular diagnostic tool, has been greatly developed in TB research. The sensitivity and specificity reported for predicting single common anti-TB drugs have been over 80% (7,8), but few studies evaluated the prediction of MDR and XDR based on WGS.

This study has been proposed to quantify the cost effectiveness of the whole genome sequencing, as it is important aspect to be considered while formulating any policy, and uptake of new intervention.

Figure 1: Integrated Diagnosis and Treatment Algorithm for Tuberculosis (9):

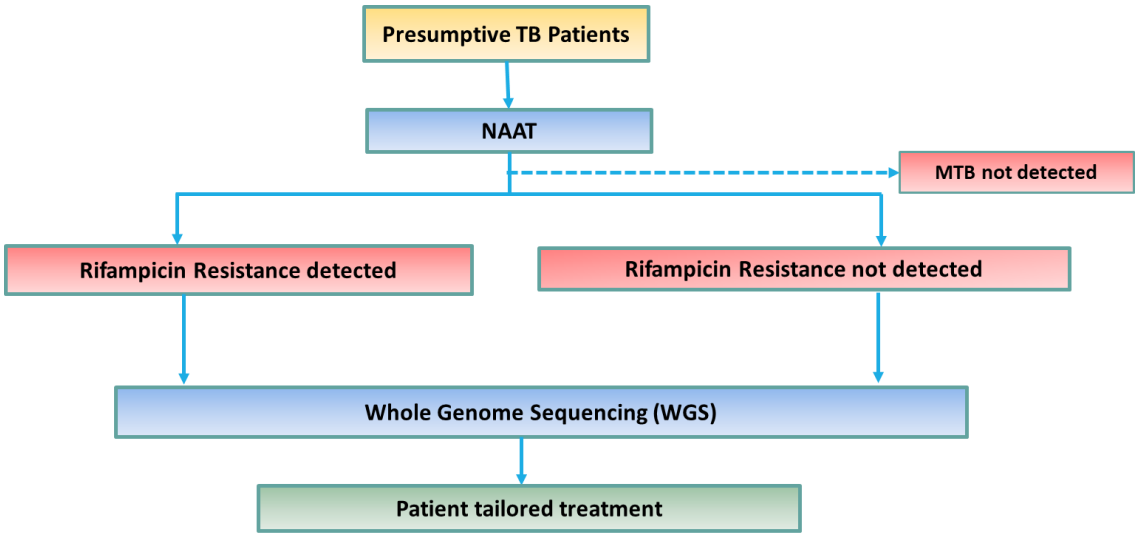


Laboratory turn-around time: The various diagnostic techniques used in TB diagnosis differ substantially in the timing to provide the results (Table 1). As per treatment algorithm these tests needs to be applied in series or parallel for reaching the final diagnosis. The proposed intervention of Whole Genome Sequencing can bypass the traditional tests (Figure 2) such as line probe assays, and culture-based sensitivity tests to facilitate the diagnosis of the DR-TB, MDR-TB and XDR-TB.

Table 1: Laboratory turn-around time for various tests.

Test	Laboratory turn-around time
CBNAAT	2 hours (testing time)
Truenat	1 hour for TB detection and 1 hour for rifampicin resistance
Line probe Assays for drug resistance	1-3 days
Drug sensitivity test (liquid medium)	1-3 weeks from positive culture
Complete genome profiling/ Whole genome sequencing	7-8 days

Figure 2: Proposed sequencing of workflows for TB diagnosis and initiation of treatment using Whole genome sequencing (WGS)



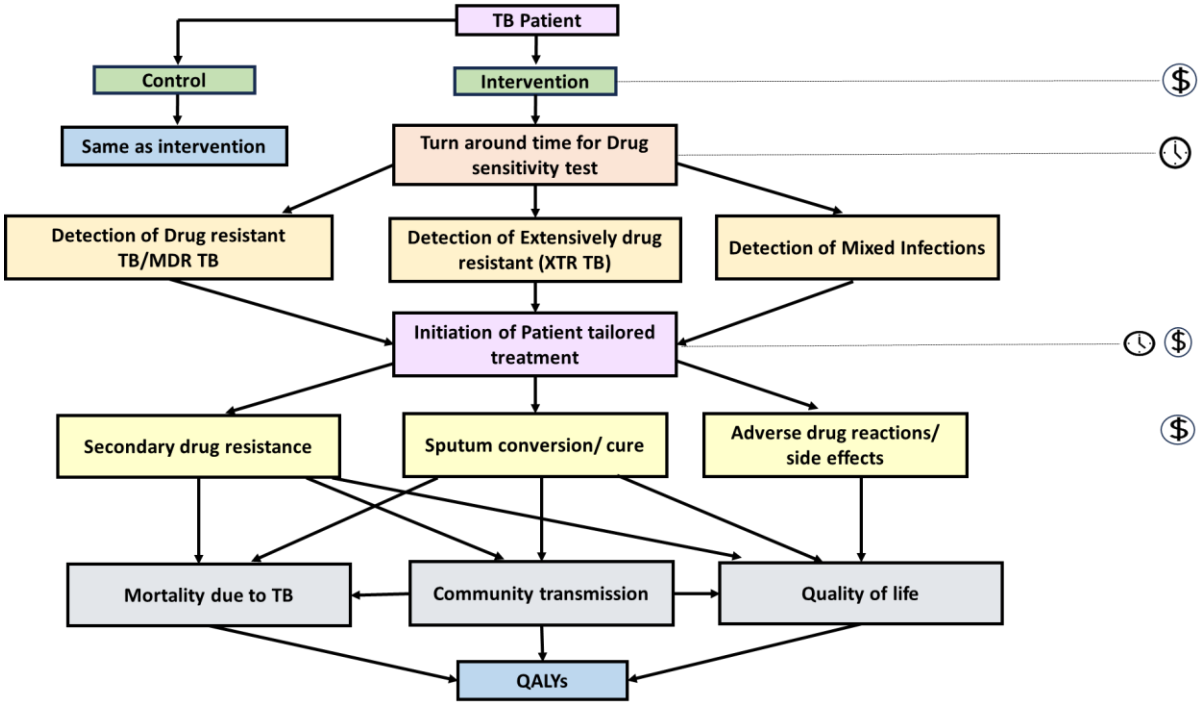
Research question:

Is using Whole Genome Sequencing in place of current practice of molecular testing by line probe assays and Culture based drug sensitivity to detect the drug resistance in TB patients cost-effective in India?

Objectives:

- To assess the feasibility of implementation of the Whole Genome Sequencing in India
- To assess the change in time to initiate patient tailored treatment by using WGS as compared to the current practice.
- To assess the incremental cost per additional community transmission case averted by using WGS as compared to the current practice.
- To ascertain the incremental cost per life year gained with the use of WGS as compared to the current practice.
- To ascertain the incremental cost per Quality adjusted life year gained (QALY) gained with the use of whole genome sequencing as compared to the current practice (FL-LPA, SL-LPA, LC DST).

Conceptual Framework:



Proposed Methodology:

To assess the feasibility of implementation of Whole Genome Sequencing, Landscape analysis will done by review of literature, and key informant interviews.

The proposed methodology for the economic evaluation is model based cost-utility analysis.

Population: All diagnosed TB patients by CBNAAT/TrueNat

Intervention: Universal Drug susceptibility testing (UDST) using Whole genome sequencing

Comparator: Current practice

- First-line Line probe Assay (FL LPA)
- Second-line Line probe Assay (SL LPA)
- Liquid Culture Drug Sensitivity Test (LC DST)

Outcomes: The following intermediate and long-term outcomes have been proposed:

Intermediate outcomes:

- Change in duration of illness due to early initiation of patient tailored treatment
- Change in secondary drug resistance due to early initiation of patient tailored treatment
- Change in adverse drug reaction due to early initiation of patient tailored treatment

Long term Outcomes:

- Change in community transmission
- TB attributed mortality
- Quality of life
- Life years and QALYs

Budget Impact:

- Incremental cost of inclusion of WGS in NTEP

Model Overview:

Time Horizon: A time horizon of 24 months will be considered.

Cycle length: One month of cycle length will be used for the analysis.

Perspective: The analysis will be done both from Health system perspective and Abridged societal perspective.

Discount Rate: A discount rate of 3% will be applied to both costs and consequences.

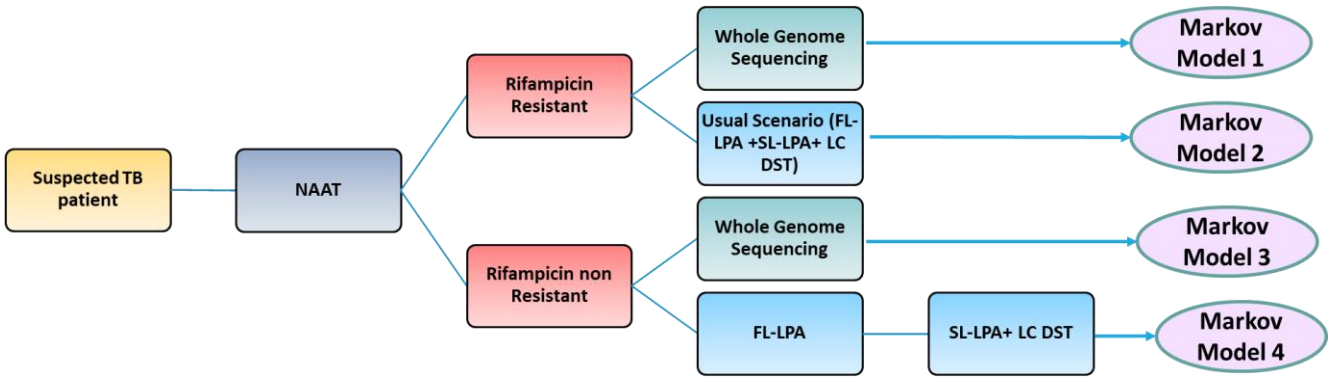
Model: Combination of Decision Tree, Markov Model, Time to event analysis, and SIR (Susceptible, Infection, Recovered) Model will be used for the economic evaluation.

Decision Tree: Decision tree will be used to obtain number of drug sensitive (DS) TB patients, Multi drug resistant (MDR) TB patients and to ascertain number of days to initiate personalized (Anti-tubercular drug) ATD regimen. TB suspected patients will undergo NAAT test first, and based on their resistance status either undergo Line probe assays and culture-based drug sensitivity tests serially in case of resistant, or among non-resistant they might undergo first line probe assays then parallely followed by second line probe assay and culture based dug sensitivity tests. However, in intervention arm, After NAAT irrespective of the rifampicin resistance status, all patients undergo whole genome sequencing.

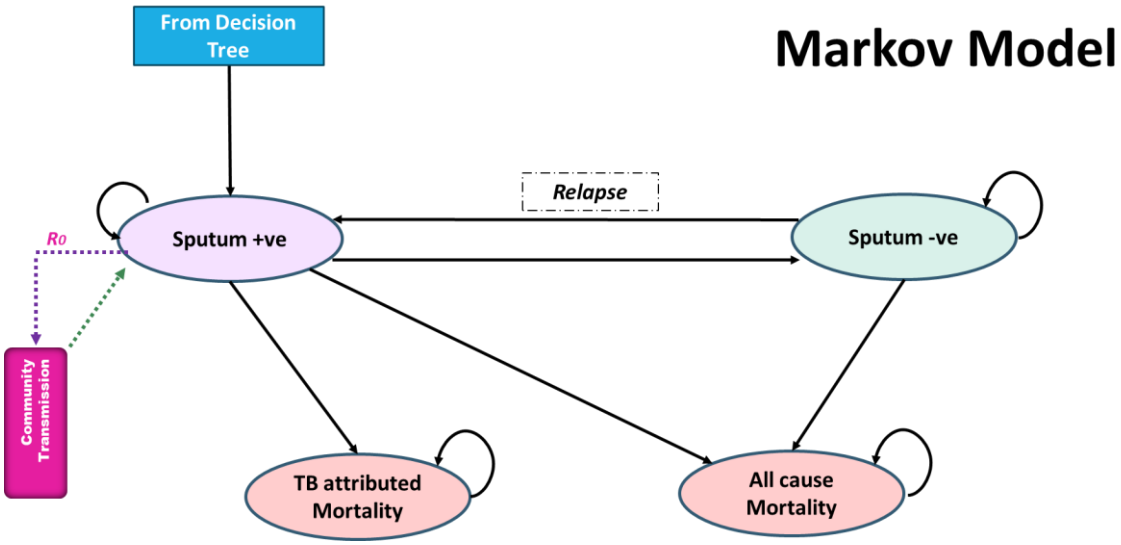
Markov Model: The sputum positive patients from decision tree will enter to Markov model. The Markov model will be used to estimate health outcomes in DS TB, MDR TB, and duration of sputum conversion in DS TB, MDR TB patients.

Time to event Analysis: To obtain the **t**ime specific conversion rates in DS TB, MDR TB patients, time to event analysis will be employed.

SIR Model (Susceptible, Infection, Recovered) Model: To ascertain extent of community transmission from DS TB, MDR TB patients



Markov model:



Assessment of costs:

Cost of Diagnosis: The costs of diagnosis for the comparator arm will be obtained from the analysis of secondary literature. The cost of diagnosis using the intervention (Whole Genome Sequencing) will be done by primary data collection at PGIMER, Chandigarh.

Cost of Treatment: For treatment costs both health system costs and out of pocket expenditure will be included. Health system costs will be obtained from National Health System Cost Database. The price of the drugs will be obtained from Central TB Division. For data on out of pocket expenditure, analysis of primary data of TB patients from Madhya Pradesh will be done.

Valuation of consequences: The Effectiveness parameters will be obtained from published literature. For parameters related to sensitivity and specificity, published literature in form of systematic review or meta-analysis will be considered**.** The parameters related to Turn-around time, secondary resistance, ADR and side effects of respective ATDs, Sputum negativity rate will be obtained from the published literature. Parameters on Quality of life will be obtained

from analysis of primary data of TB patients from Madhya Pradesh, and published literature. The Unit of outcome valuation will be QALYs.

Cost effectiveness assessment: The increment cost effectiveness ratio will be calculated by determining the difference in the costs and effects.

Incremental Cost Effectiveness Ratio (ICER):

$$ICER = \frac{(C_2 - C_1)}{(E_2 - E_1)}$$

C_2 and C_1= costs of intervention and baseline scenarios respectively

E_2 and E_1= effects of intervention and baseline scenarios respectively

Scenarios:

Strategy 1: Current practice of using First-line Line probe Assay (FL LPA), Second-line Line probe Assay (SL LPA), and Liquid Culture Drug sensitivity Test (LC DST)

Strategy 2: Diagnosis by NAAT followed by Whole Genome Sequencing for Drug sensitivity test

Strategy 3: Whole Genome Sequencing alone (without NAAT)

Strategy 4: Diagnosis by NAAT followed by Whole genome sequencing in only rifampicin resistant cases, and patients who are not responsive to DS-TB regimen

Sensitivity Analysis: Univariate and Probabilistic analysis will be done for sensitivity analysis. Additionally, threshold analysis will be performed to account for the actual proportion of TB patients those are getting NAAT. The analysis will be done to account for different levels of coverage of NAAT, in order to assess at what level of NAAT coverage, Whole Genome Sequencing becomes cost-effective.

Additionally, the prerequisites for conducting the Whole Genome Sequencing and the ethical implications involved in conducting Whole Genome Sequencing will be presented in the outcome report.

Ethical Considerations:

The research ethics will be followed while conducting the research. An ethical clearance will be sought from the institutional ethical review committee. The written consent will be taken from the respondents of the interview/consultation. The participants will be informed that their participation is voluntary, no information obtained from them will be divulged to anyone other than investigator; the confidentiality of data will be strictly maintained; and failure to comply will not result in any penalties or loss of benefits. The participants will be also informed that they can contact the principal investigator in the vent of questions, comments, or complaints related to the study. All respondent identifiers were removed from the data collected before statistical analysis.

Results:

Landscape Analysis: A thorough review of literature was done, along with key informant interviews for assessing the feasibility of implementation of Whole Genome Sequencing. Key-informant interviews were done with Clinicians, Policy makers, Program Officers, and Industry partners.

The results of the study indicate that the proposed technology is contingent upon the Nucleic Acid Amplification Test (NAAT). However, the coverage of NAAT is currently low, estimated to be around 30%, and there still exists a dependency on Microscopy. This highlights a significant gap in the effectiveness of the proposed technology due to its reliance on a testing method with limited reach. The study emphasizes the need for a shift in focus towards

improving the coverage and implementation of existing strategies for tuberculosis (TB) rather than introducing newer high-end technologies.

Furthermore, the results underscore several practical challenges associated with the proposed technology. The implementation requires well-trained staff and specialized equipment, both of which are currently unavailable in the country. This lack of infrastructure poses a substantial barrier to the successful adoption of the technology. Additionally, on-field implementation of the proposed technology is not yet feasible, making it challenging to obtain cost data and evaluate the practical implications of its deployment.

A critical finding of the study is that the proposed technology, if implemented, would render the current TB testing infrastructure useless. The intention to replace existing Line Probe Assays and liquid culture drug sensitivity testing with newer whole-genome sequencers is deemed impractical due to the associated high costs and the need for a complete overhaul of the existing system. As a result, the study suggests that efforts should be directed towards enhancing the existing infrastructure rather than pursuing an approach that necessitates its replacement. Overall, the results underscore the importance of a pragmatic and context-specific approach to TB control, focusing on feasible strategies that address the current limitations of testing methods and infrastructure.

Economic Evaluation: The economic evaluation of the proposed technology faces a notable challenge as, during the landscape analysis, it was observed that the technology has not been implemented in a real-world setting. Consequently, the absence of on-field implementation precludes the collection of essential cost data required for a comprehensive economic evaluation. The inability to gather first hand data on the costs associated with the proposed intervention restricts the thorough assessment of its economic feasibility, hindering the execution of a complete economic evaluation.

Given the pivotal role of cost data in economic evaluations, the absence of on-field implementation data underscores a critical limitation in our ability to gauge the financial implications and benefits of the proposed technology. As a result, the study refrained from conducting a full economic evaluation, recognizing the importance of having accurate and context-specific cost information to make informed decisions about the economic viability of the intervention. This limitation in data availability emphasizes the need for future research to focus on real-world implementation scenarios, enabling a more robust economic analysis that can contribute meaningfully to the decision-making process surrounding the adoption of the proposed technology.

Recommendations:

1. **On-Field Implementation Constraints:**
    - Recognize the current impracticality of on-field implementation for the proposed intervention, highlighting the need for future research to explore avenues for real-world application.
2. **Strategic Focus on TB Control:**
    - Shift emphasis from incorporating untested technologies to improving the implementation of existing TB control strategies.
    - Prioritize efforts to address identified gaps in TB management, such as enhancing diagnostic reach, treatment accessibility, and healthcare infrastructure.
3. **Economic Evaluation Challenges:**
    - Acknowledge the limitation in economic evaluation due to the unavailability of cost data, emphasizing the significance of accurate financial information for informed decision-making.

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