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| **Contact:** | | Dr. Manjula Singh, ICMR, Under department of health research, MOHFW, GOI, India | | Tel: +91 9868245793 Fax: +91 26588896 Email: [drmanjulasb@gmail.com](mailto:drmanjulasb@gmail.com) |
| **Contact:** | | DG, ICMR, Indian Council of Medical Research, (ICMR) India | | Tel: Fax: +91 26588896 Email: [dg@icmr.org.in](mailto:dg@icmr.org.in) |
| **Contact:** | | Dr. Saurabh Gupta AIIMS, Delhi, India | | Email: [drsaurabhmd@gmail.com](mailto:drsaurabhmd@gmail.com) |

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| **Abstract:** | In 2017, 27% of the estimated 10 million global Tuberculosis (TB) cases developed in India. In the past few years, India has been actively implementing multiple strategies for reducing the burden of TB, including the web-based reporting system, the national TB prevalence survey, and the rollout of TB service delivery from all HIV clinics. An early adoption of Computer Assisted Diagnosis (CAD) systems based on artificial intelligence (AI) technologies for TB detection in India will synergize with the current endeavours to close the gap in TB control and will help global fight against TB and use of AI in the field of population health.  This TG works in the standardization of bench marking approach for development of AI tool for radiographic detection and screening of TB. |

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# Introduction

Machine learning (ML) techniques have been used world-wide for improving public health through development of better prognostic, diagnostic and predictive models. The application of ML technologies in healthcare has increased exponentially. In 2017, 27% of the estimated 10 million global TB cases were reported from India. There is a need to detect the missed cases by early adoption of CAD systems based on artificial intelligence (AI) technologies for TB detection. This will synergize with the global endeavours to close the gap in TB control. .

ICMR has access to large volume of high quality clinical data from various extramural and intramural programs. The data ranges from text based patient profiles to complex molecular sequences and structures and images. The proposal focuses on development of the AI tool for radiographic detection and screening of TB and will nucleate advance machine learning and analytics on data generated from various TB research activities of ICMR.

## Document Structure and description

Description of topic: The topic deals with the development of an AI tool for radiographic detection of TB. In 2017, 27% of the estimated 10 million global TB cases developed in India. 1 In the past few years, India has been actively implementing multiple strategies for reducing the burden of TB, including the web-based reporting system, the national TB prevalence survey, and the rollout of TB service delivery from all HIV clinics. An early adoption of CAD systems based on artificial intelligence (AI) technologies for TB detection will synergize with the current endeavors to close the gap in TB control around the world and will help in the global fight against TB and use of AI in the field of population health.

Artificial intelligence technologies, including deep learning (DL) and natural language processing (NLP), draw attention of many public health professionals because of its potential to ease the shortfall of health workers.4 In India, the quality of TB care varies widely depending on the geographical location and the socioeconomic status of a patient, resulting in delayed or missed diagnosis of active TB cases.5

There is approximately only one radiologist for every 100,000 population in India. In Zambia, also one of the high-TB/HIV-burden countries, there are only two radiologists in the country of over 11 million population.3 The national goal to eliminate TB in India by 2025 and around the world by 2030 can be facilitated by early adoption of AI in TB control program, and successful use of AI in ending TB will help the world achieve the goals.

There are various AI tools in development in India and there is need to have a robust AI tool with a high sensitivity and specificity which can be used as a screening tool. This document is intended to propose a benchmark for AI in radiographic detection of Tuberculosis which include data format, desired data for AI training and testing as well as AI performance evaluation methodologies.

## Relevance

The topic is of immense relevance in view of following:

1. AI technologies, including deep learning (DL) and natural language processing (NLP), draw attention of many public health professionals as it can overcome the shortage of healthcare professionals. Based on the study conducted by the Center for Internet and Society, India (CISI), it is evident that India has a well-established infrastructure for integration of AI into the Indian health technology infrastructure.
2. AI has gained a platform in India to enable the scientific community to deal with challenges related to cognitive disorders and social issues through the use of psychological tools & batteries, early diagnosis and better therapies, intervention technologies and rehabilitation programs.
3. India has conducted mobile TB diagnostic van intervention using X-ray diagnostic vans and sputum microscopy for diagnosis of TB in tribal population which has resulted in increase in detection and reduction in out of pocket expenditure of patients . The AI technique can help in diagnosis of TB cases in difficult o reach areas in India and other low income countries.
4. Also National TB prevalence survey is being conducted covering 500000 population in entire coutry using mobile X-rays in field. The AI x-ray diagnosis would be of immense use in field diagnosis of TB and can be used across the globe in other countries as well where there are limited resources and expertise.

## Current approaches and Gold Standard for detection

The gold standard for diagnosis of TB is the microbiological confirmation either by culture or CBNAAT. The sensitivity of the smear microscopy is low and it tends to miss many cases of TB and the availability of the CBNAAT is not there in peripheral areas because of the infrastructure that it requires and lack of expert manpower to run it and of course the high cost. X-rays are done to further confirm the findings. Therefore role of X-ray becomes more important specially as the triage test to detect the TB cases and moreover, the availability of the X-ray machines in the periphery make is more feasible. Currently the X-rays are read by the radiologists and co-related clinically. However in resource poor countries use of AI can help in radiographic detection of TB at a very low cost thus making a huge impact in saving lives.

## Possible impact of AI on this Topic

Pulmonary TB being an infectious disease has the threat to spread in absence of its timely detection which is a major challenge. The current diagnostics available make it more challenging as many millions across the world are missed by the conventional method. Use of AI for radiographic detection of TB would have greater public health impact around the world in view of its potential to be used in remote areas for detection of TB.

## Expected Impact of the benchmarking

The benchmark dataset for the X-ray detection of TB should be representative of not only of one region but the entire world to be robust enough to have >95% sensitivity and 100% specificity. The benchmarking for the AI tool would help in generating such a dataset which could help in validation of AI tool across the world.

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## Ethical considerations

* **Ethical consideration of benchmarking including its data acquisition**: Ethical considerations on collection of data and thereafter usage of AI for public health are very important. The major concern is about the data anonymization. The identifiers must be removed from the data and the data used for learning should be confirmed via gold standard tests. The data acquisition should be voluntary from the cases and their contacts. Consent of patients for use of the data for development of AI tool must be taken.
* **Ethical consideration for use of AI tool for public health use:** The radiographic detection of TB using AI must be 100% specific and >95% sensitive. Primarily the tool could be used for screening purposes in remote settings followed by the final diagnosis by other methods. The patients must be informed of the use of such tools for screening and detection of their disease and their implications.

# Existing AI solutions

There are few AI tools available for radiographic detection or screening of TB. But they have been trained on a limited data set and the entire range of variables have not been covered. Some of the systems have very low specificity and thus more false negative cases would be detected. These tools tend to fail on the undisclosed data sets. Therefore there is a need for a standard benchmarking for the training and testing the data sets.

## Existing work on benchmarking

There have been discussion on having a need for a benchmarking in area of AI for health but for the radiographic detection of TB, there is no benchmarking done till now. The tools available have been trained on the data set that was made available to hem mostly hospital based.

# AI4H Topic group: Current topic group and its mandate

The current topic group is specific and relevant to AI4H. The objectives are:

1. to provide a forum for open communication among various stakeholders,
2. to agree upon the benchmarking tasks of this topic and scoring metrics,
3. to facilitate the collection of high quality labeled test data from different sources,
4. to clarify the input and output format of the test data,
5. to define and set-up the technical benchmarking infrastructure, and
6. to coordinate the benchmarking process in collaboration with the Focus Group management and working groups.

The primary output of a topic group is one document that describes all aspects of how to perform the benchmarking for this topic. (The document will be developed in a cooperative way by suggesting changes as input documents for the next FG-AI4H meeting that will then be discussed and integrated into an official output document of this meeting. The process will continue over several meetings until the topic description document is ready for performing the first benchmarking.)

This Topic Group is for building AI based solution for radiographic detection of Tuberculosis.

# Method

The method for AI benchmarking includes input data format requirement and output data, testing data, labelling and testing and scoring matrixes

## AI Input data

Chest X-Ray images obtained from culture confirmed (Gold standard) cases have been included for AI benchmarking. Besides normal X-rays from various geographic locations, and confirmed Non-TB cases like pneumonia, Bronchitis etc have been included. Labelled imageswould be required.

## AI output data structure

The AI output should include AI tool detecting the TB lesion position, area, classification and differentiating from Normal X-rays and Non-TB cases.

## Test data labels

* 1. For clinical evaluation of AI algorithm for radiographic detection of Tuberculosis, images would be obtained from confirmed cases of TB and images labelled by Expert panel. The panel would involve at least two experts with more than 10 years of practice in chest radiology. In case of any discrepancy among the two radiologists, the image would be referred to the third radiologist for final decision on disputed annotations from the other experts. All experts would receive prior specialized training regarding how to annotate TB lesions (including cavitary lesions) and lesion boundaries etc.
  2. For clinical evaluation of cases for AI for radiographic detection of TB, gold standard is the microbiological confirmation of cases i.e either by sputum culture confirmation, CBNAAT confirmation or confirmation by clinical follow-up. The data set would also include cases from non-TB conditions which would include pneumonia, asthma, bronchitis stc.
  3. Confidentiality of gold standard testing data results would be maintained.

## Model development

The model will be developed in following stages -

* **Stage 1:** Building an algorithm that interprets chest plain radiography and detects signs of pulmonary tuberculosis
* **Stage 2:** Building a more comprehensive algorithm that combines imaging and other clinical information to provide more reliable prediction for diagnosis of tuberculosis
* **Stage 3:** Expanding the model to be used in detection of other pulmonary diseases

Each stage will consist of three sub-phases;

* **Phase 1:** Retrospective data collection and model building
* **Phase 2:** Prospective validation and user feedback
* **Phase 3:** Full deployment of the system and continuous improvement

## Scores and Metrices

Testing

* To evaluates AI tool’s performance Dataset comprising of a mix of each confounding variable case test data would be taken and tested against performance of AI. The initial diagnosis would be lto differentiate normal with an abnormal ones and then TB and Non-TB. Further types of TB like cavitary, military, and lobes affected etc. would be differentiated.
* **Primary Benchmarking:** Primary testing would include detection of abnormal X-rays from normal X-rays from overall dataset. Abnormal X-rays would be further classified as TB and Non-TB based on detection of TB lesion. The data would also include normal X-rays and also X-rays from other non-TB cases. TB lesions detected by AI tool, would be compared with pre-labelled lesions to determine the true positive and false positive cases. Benchmarking metrics would include sensitivity of the tool to detect TB cases based on TB lesions and false positives. Initial detection would be between normal and abnormal cases and further classification would be for tuberculosis based on which sensitivity would be calculated. Specificity would be calculated based on ability of the AI tool to detect identify non-TB cases as Non-TB.
* **Secondary Benchmarking:** This would involve marking the lesion size, area, cavity, classification etc. Early cases of TB can be easily missed if not seen by experienced radiologists. Therefore, confirmed cases with early lesions in X-rays marked by radiologists from confirmed TB cases would be included to train and test the performances.

## Available data sets and undisclosed test data sets

1. In order to assess algorithm robustness, sufficient and diversified data from multiple heterogeneous sources (e.g., various types of digital images like, digital and Biochemical films converted into digital images, patient demographics like age, sex, socioeconomic status, geographical areas, smokers and other clinical conditions, etc.) would be used for testing to verify the generalization capacity of AI. Public and real-world undisclosed data (desensitized) would be collected.
2. Database currently would includes 69000 X-Ray images from a community base TB prevalence survey done in one of the states in South India which includes culture confirmed cases and normal X-rays. The Images Collected from various TB studies would also be included. The data set would also include the X-ray images from the ongoing National TB Prevalence survey which included 500,000 x-ray images to be collected from 625 clusters from all the states of the country over a period of one year. This would cover the geographic differences (rural and urban, plain and plateau etc.), gender differences, cases with different socioeconomic status and lifestyles. Data from various studies would come from multiple hospitals (Public and private).
3. The training data set would comprise of 80% of the entire data set and undisclosed test data would include 20 percent of the entire data set. The data sets would cover the entire variations as discussed above.
4. The entire data set would also have confirmation of cases by Gold standard test (microbiological or clinical).
5. The AI tool would be further validated in a prospective manner by the community based and hospital based study wherein the initial diagnosis of a new TB suspect would be given by the AI tool based on X-ray findings which would be further confirmed by radiologists, microbiological tests and clinical follow-up.
6. A panel of Radiological and Pulmonary experts will examine labelled undisclosed test data to confirm data variance, quantity, heterogeneity, labelling and conformity to ethical and legal requirements.

## AI tool development and status

ICMR, under DHR, Govt. of India, currently has large amount of data clinical and Pictorial generated through its 33 permanent Institutes and regional Research centers and also through ICMR funded studies. ICMR also has extensive clinical expertise in developing AI tool for diagnosis or screening of various communicable and non communicable diseases and is in a position be to lead the study. We are currently collaborating with Institute of Plasma Research (IPR), Under Govt. of India for the development of the AI tool for radiographic detection of TB. The IPR has vast infrastructure and expertise in developing the tool for the Public health use. They have already developed the tool which can differentiate between TB and normal cases.

**Features of AI tool:** The automated tool can automatically detect foot print of Pulmonary Tuberculosis in Chest X ray at a rate of10 images per minute, can identify different form of tuberculosis; can differentiate normal X ray from abnormal X ray using images of both biofilms as well as dicom version of digital X ray to some extent. The software also had an added advantage of being cloud independent and can be used in common desktops and laptops.

The process of training of the tool for detection of TB is in process. The tool would further be tested in a prospective study.

Salient features of the strategy to develop AI would be:-

* + - 1. The tool must be trained to identify all possible variant of pulmonary tuberculosis.
      2. Tool must have high sensitivity as well as specificity. Maximum tuberculosis cases should get screened out and no non tuberculosis case be identified as tuberculosis.
      3. Tool must be able to screen tuberculosis considering all possible variation in subject/chest X ray film as per geography, age, sex, occupation, stage of tuberculosis, quality of image, type of image.
      4. Tool can be used in remote areas with minimal manpower.
      5. Chest X ray films closely resembling tuberculosis but are non-tubercular in nature should ideally be screened as negative.

## Reporting Methodology

* Reporting metrics would be two staged; first stage the AI tool would differentiate between Normal and abnormal. Normal cases would be true normal cases and the accurate detection would define specificity.
* Second would be abnormal but TB or Non-TB. This would define the sensitivity of the tool.
* Later on the tool can be trained to detect other non-TB chest lesions like pneumonia, Bronchitis etc.

## Results

Data is being collected at present

## Discussion

NA at present

## Expected outcome

Development of a Cost-effective AI tool for radiographic diagnosis for early detection of TB

## Declaration of Conflict of Interest

None

# Response to call for contribution to the Topic Group Tuberculosis:

Our Topic group got immense participation from various researchers from Various countries:

* + - 1. Anushikha Singh, PhD student, IIT Delhi: Working on the project ‘Validation and Fine Tuning of the Computer Aided Diagnosis of Pulmonary Tuberculosis Model for the Indian Subcontinent".

She used total Images 550 (healthy images -216 & TB affected images- 334): All these experiments were performed on Indian dataset having. 75% Images were used to train the model and 25% images were used to test the performance of model. These images were provided by CMC Vellore Hospital.

* Deep learning based approach for classification of healthy and TB affected chest x-rays
* Pre-trained Resnet model provides 98.60% Sensitivity and 87.90% Specificity
* Pre-trained Alexnet model provides 98.60% Sensitivity and 83.30% Specificity
* Pre-trained Googlenet model provides 92.90% Sensitivity and 84.80% > Specificity

Classification of healthy and TB affected chest x-rays based on hand crafted features

* Graph cut based method was used for lung segmentation from chest x ray image and then pattern features were extracted from segmented ling images. These features were fed to random forest classifier for classification of healthy and TB affected chest x-rays. The experiment were performed on china dataset having Total Images - 662 (healthy images -326 & TB affected images- 336). 70% Images were used for training and 30% images were used to test the performance of classifier. Classification accuracy for the above mentioned dataset was 91%.
* Graph cut based method was used for lung segmentation and Gabor filter was used for localization of ribs in the image. Clinically informative features were extracted and further fed to random forest classifier for classification of healthy and TB affected chest x-rays. The experiment were performed on indian dataset having Total Images - 550 (healthy images 216 & TB affected images- 334). 70% Images were used to train the model and 30% images were used to test the performance of classifier. Classification accuracy for the above mentioned dataset was 67%.
  + - 1. **Dr. Cristina Curreli**, a research fellow at the University of Bologna currently working at the Biomechanics group held by Prof. Marco Viceconti under the project "In Silico Trial for Tuberculosis Vaccine Development" funded by the EU. The main goal of the project is to **develop computer simulations and models that can be used to reduce the costs of the clinical trials required to test the efficacy of new therapies for tuberculosis**. Involved in the design of the in silico clinical trial, in the verification, validation and qualification process of the resulting in silico method with the European Medicine Agency.

* + - 1. **Dr. CK Chen, CEO Infervision**, a company focusing on Medical Artificial Intelligence. Infervision is currently medical AI companies around the world. Infervision is also the ITU focus group **topic driver for AI for Volumetric Chest Computed Tomography**. They are currently working with China CDC and a few Chinese provincial governments to provide Tuberculosis X ray screening AI solutions for remote areas where it is very difficult for human doctors to penetrate and operate daily. Considering AI application in Tuberculosis is a very meaningful step towards solving the global TB problem, especially in remote and less developed regions where is difficult to find enough well trained doctors and physicians, expressed desire to contribute to the solution.
      2. **Dr. Jogundas Armaitis, cofounder of Oxipit**, a company applying AI to chest X-rays. Oxipit is a producer of a **CE marked medical software** suite that is in use in several clinics in Europe. Their **software generates preliminary radiological reports from chest X-rays covering 75 findings, TB being one of them**. They recently participated in the UNAIDS Health Innovation Exchange and sae a strong need for reliable automatic TB detection software. Therefore, creating a proper vendor-independent benchmark, looks as a worthy endeavour.
      3. **Dr. Darlington Shingirirai Mapiye**; A technical lead for the data driven healthcare team **at IBM Research Africa.** The main objective of the IBM Research is to tackle Africa's grand challenges with a particular focus on AI. They are currently working on TB and Cancer. In TB, they are currently working on two projects:

Machine Learning approaches for Drug resistance profiling and this work is in collaboration with a TB reference lab,

* + - * Deep learning to look at molecular markers for TB treatment progression or regression from chest x-ray images and
      * Tb transmission dynamics focusing on network analysis and machine learning.

1. **Dr. Morten, Head of the TB program at FIND,** a global non-profit organization driving innovation in the development and delivery of diagnostics to combat major diseases affecting the world’s poorest populations. Their work bridges R&D to access. They have deep technical and practical experience in the definition of needs, development of fit-for-purpose products, generation of evidence for regulators and policy-makers, analysis of market dynamics, the introduction of new products, and strengthening of laboratory systems. AI enabled diagnostic solutions is a central area of focus in their strategy and they are interested in joining the group.

In addition, two companies in South Africa, (Under BRICS collaboration) are in discussion with ICMR for testing of two CAD tools in National TB Prevalence Survey currently being undertaken by ICMR.

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