Screening and Triage for TB using Computer-Aided Detection (CAD) Technology and Ultra-portable X-Ray Systems: A Practical Guide

Table of Contents

Abbreviations

ACF	Active Case Finding
AI	Artificial Intelligence
AP/PA	Antero-posterior/ Postero-anterior
AUC	Area Under the Curve [ROC curve]
CAD	Computer-Aided Detection
CXR	Chest X-ray
DICOM	Digital Imaging and Communications in Medicine
GDF	Global Drug Facility
FIND	Foundation for Innovative New Diagnostics
NNT	Number [of people] Needed to Test
NPV	Negative Predictive Value
NTP	National Tuberculosis Programme
ICT	Information and Communication Technology
ITSC	Iterative Threshold Score Calibration
PACS	Picture Archiving and Communications Systems
PII	Personally Identifiable Information
PPV	Positive Predictive Value
PRAUC	Area Under the Precision Recall Curve
PRC	Precision Recall Curve
RIS	Radiology Information System
ROC	Receiver Operating Characteristic [Curve]
RFQ	Request for Quote
SOP	Standard Operating Procedure
TB	Tuberculosis
WHO	World Health Organization
Xpert	GeneXpert MTB/RIF test

Acknowledgements

This guide was written and coordinated by Zhi Zhen Qin (Stop TB Partnership), with support from Rachael Barrett, Jacob Creswell, and Wayne van Gemert (Stop TB Partnership). Section 1.2, 5.1, Annex 1 and 9 received critical input and review from Rory Pilgrim, Rayman Huang, and Yun Liu (Google LLC), and Santosh Bhavani (Amazon.com, Inc.). Section 4.6 was jointly drafted by Brian Citro (Privacy Lawyer & Independent Researcher). Annex 6 and Annex 7 received critical input from Cristina Celan (Center for Health Policies and Studies, Moldova). Section 4.8 received critical input from Shibu Vijayan (PATH India, an early implementer of CAD software supported by Stop TB Partnership's TB REACH). Critical review was provided by Estelle Petiot and Magali Babaley (Stop TB Partnership), Cecily Miller, Maria del Rosario Perez, Francesco Ribolzi (WHO), Morten Ruhwald, Sandra Kik, and Kavindhran Velen (FIND), William Wells (USAID), Claudia Denkinger (Heidelberg University), as well as early implementers with the support from Stop TB Partnership's TB REACH: Monde Muyoyeta (Centre for Infectious Disease Research, Zambia), Andrew Codlin (Friends for International TB Relief, Vietnam), Shibu Vijayan (PATH India), Cristina Celan (Center for Health Policies and Studies) and Laura Belous (Phthisiopneumology Institute "Chiril Draganiuc", Moldova), Shifa Habib (Community Health Solutions, Pakistan).

Development of this document was made possible with financial support from the United States Agency for International Development, and Global Affairs Canada. The views expressed herein are those of the authors and do not necessarily reflect those of the U.S. Agency for International Development, the U.S. Government, or Global Affairs Canada.

About the guide

This guide provides practical guidance on how to implement computer aided detection (CAD) technology and ultra-portable digital X-ray systems for TB screening and triage. It includes advice on how to convert World Health Organization (WHO) policy guidance into a practical implementation plan, building on initial field experience gained by early implementers. This experience is presented in several case studies that identify lessons learned and challenges that arose. This guide offers various technical explanations of the newly added products available in the Stop TB Partnership's Global Drug Facility (GDF) catalogue and relevant implementation resources, including a high-level checklist of vital implementation steps and budgetary considerations, technical specifications for use during procurement, and checklists for site assessment.

The guide is structured so that:

- **Chapter 1** provides an overview of CAD technology, including the place of CAD in diagnostic algorithms, international policy on the use of CAD, the technology behind CAD, an overview of the CAD product landscape, and how to understand the output of CAD – and CAD accuracy.
- **Chapter 2** discusses key implementation considerations when deploying CAD technologies, including the hardware, software, server and internet requirements. This chapter describes the selected CAD products included in Stop TB Partnership's GDF catalog and pricing information.
- **Chapter 3** introduces ultra-portable X-ray systems available through the GDF procurement mechanism, discussing the core components and accessories, key implementation considerations including portability, electrical power, console and radiation safety. This chapter also discuss all the configurations and pricing of integration of the CAD software with the ultra-portable X-ray systems (with a comparison of all possibility hardware and software combinations).
- **Chapter 4** describes key programmatic steps and considerations for the implementation of CAD and ultra-portable X-ray systems, including situation assessment, stakeholder framework, registration, site preparation and assessment, data privacy and security, installation, training and capacity building as well as monitoring and evaluation. The chapter also introduces several resources (provided below as annexes to this guide) that will help implementers to follow the relevant recommendations.
- **Chapter 5** provides a closer look at threshold score selection strategies for CAD software users and details several alternative strategies for consideration.
- **Chapter 6** highlights the experiences of some early implementers of CAD with ultra-portable X-ray systems.

The guide will be periodically updated to reflect product updates, ongoing experience, and to include any relatively straightforward techniques and tools that could be more widely adopted. Please contact the authoring organization to suggest any contributions to this guide.

Target audience

The guide is for use by health officials, programme managers, testing site managers, IT professionals, radiologists, radiographers, clinicians – working nationally, regionally, or at individual sites – as well as technical partners and donors.

About Stop TB Partnership

The Stop TB Partnership is a unique United Nations hosted entity based in Geneva, Switzerland, committed to revolutionizing the tuberculosis (TB) space to end the disease by 2030. The organization aligns more than 2,000 partners worldwide to promote cross-sectoral collaboration. The Stop TB Partnership's various teams and initiatives take bold but measured risks to identify, fund and support innovative approaches, ideas, and solutions to ensure the TB community has a voice at the highest political levels and that all TB-affected people have access to affordable, high quality, and people-centered care. **Learn more at www.stoptb.org and follow us at @StopTB.**

The Stop TB Partnership's **TB REACH**, established with an initial award from Global Affairs Canada in 2010, has funded ground-breaking approaches and technologies to support the Stop TB Partnership's global mission, including digital technologies such as CAD and ultra-portable digital X-ray systems. TB REACH combines fast-track, results-based financing and rigorous, external monitoring and evaluation, so that other donor agencies and national governments can scale up successful approaches and maximize their own investments.

The Stop TB Partnership's **Digital Health Technology Hub (DHT Hub),** a unifying virtual platform that brings together the organization's expertise and work in the digital health technology space to support the achievement of the United Nations High-Level Meeting on Tuberculosis (UNHLM on TB) commitments and targets.

Chapter 1 Computer-Aided Detection of TB

There is a large, persistent gap in global TB case detection. In 2019, an estimated 10 million people fell ill with TB globally, but only 7.1 million of these people were diagnosed and notified.[1] Chest X-ray (CXR) is a recommended and commonly used tool for case detection,[2] but its effectiveness in resource-constrained settings is hampered by limited specificity, significant inter- and intra-reader variability and lack of reproducibility, as well as a lack of access to sufficiently trained radiologists.[3]

Computer-aided detection (CAD) presents an opportunity to improve the detection of TB by circumventing inefficiencies in the interpretation of CXR images, automating and standardizing X-ray interpretation, and supplementing existing human health workers. When used in combination with ultra-portable X-ray systems, the promise of CAD technology can be extended to hard-to-reach key populations (see Chapter 3).

This chapter begins by examining global policy on the use and role of CAD in TB diagnostic algorithms before shedding some light on the artificial intelligence (AI) technology behind CAD (Section 1.2, which readers may choose to skip). Finally, the chapter introduces CAD products (their input, output, and integrations), as well as concepts referred to throughout the guide, before discussing the validation thus far of CAD.

Section 1.1. Global Policy and Use Cases of CAD Software Programmes

In March 2021, the World Health Organization (WHO) recommended for the first time that CAD software programmes may be used in place of human readers for the interpretation of digital CXR in **screening and triage for TB disease:**[4] "WHO recommends that CAD may be used for the interpretation of antero-posterior or postero-anterior views of **digital plane CXR** for pulmonary TB in **individuals aged 15 years or more**. This recommendation applies to software brands that are found by external evaluation to perform at least as well as the products reviewed by the Guidelines Development Group in 2020".[1]

> 10. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease *(new recommendation: conditional recommendation, low certainty of evidence).*

However, it must be borne in mind that there is insufficient evidence to support the use of CXR alone for TB diagnosis. It therefore clearly follows that, although CAD software offers a valuable tool for the interpretation of CXR, it cannot be relied upon **– alone –** as a diagnostic tool. All diagnostic decisions should be **confirmed** by bacteriological tests and a physician's review of all clinical evidence.

Position of CAD in the diagnostic algorithm

The WHO recommends that CAD can replace a human reader in two broad contexts: for screening, and for triage.[4,5] In both, the end goal is the same, namely, that CAD be used to establish whether or not an individual should receive confirmatory diagnostic tests.

[1] From WHO Consolidated Guidelines on Tuberculosis Screening

Screening: CAD can be a valuable tool for screening individuals with or without symptoms or significant risk factors for TB, as in prevalence surveys or active case finding situations. Screening often involves the search for early disease in populations with a low risk of having TB and/or poor access to health services.

Triage: Triage tests are used in people with TB symptoms, signs, risk markers and/or test results, generally among those seeking medical attention in healthcare facilities or referred through screening or contact investigation.

Other use cases where CAD can work with human readers

AI is commonly described as a way to replace human health workers. Such a view is rather simplistic, however, and this guide does not endorse it as an ambition. On the contrary, it is important to acknowledge that there are multiple potential synergies between radiologists and CAD. For example, CAD can:

- help radiologists optimize their workflow,
- alert human readers to abnormal images requiring prioritization,
- perform pre-reading assistance,
- provide reporting assistance, and
- provide quality control,
- assist teleradiology and telemedicine service.

Section 1.2. Basic Artificial Intelligence Principles

This section tackles the basic concepts behind AI, machine learning, and CAD. Inevitably, this borrows heavily from computer science and statistics, so readers concentrating on the public health and implementation aspects of this technology may choose to scroll down to Section 1.3.

First, a few basic concepts must be introduced:

Artificial Intelligence (AI)

At its simplest, AI is intelligence demonstrated by machines (whether software or hardware). It falls into two categories: "general", or "narrow".[6] General AI (also known as "strong" AI), which aims to replicate the complexity of human consciousness, is essentially a philosophical construct enthusiastically explored in science fiction. By contrast, narrow AI, the type increasingly applied in practical applications, works on a particular task, such as driving a car. It attains that kind of capability after "learning" from huge datasets (machine learning, see below). Narrow AI is increasingly common in transport, finance, education and healthcare.[7,8] Common uses include self-driving cars, personalizing film and music recommendations, or the discovery of treatments and drugs. Following approval by the WHO in 2021, narrow AI is increasingly used in the context of TB context for the detection of abnormalities on chest X-rays. There are also a number of other AI-based technologies already used in radiology for applications unrelated to TB (for X-ray, CT or MRI scans).

Machine Learning

Machine learning is a field of computer science that uses statistical techniques to enable computer systems to "learn" from training data, without being explicitly programmed to do specific tasks.[9]

Deep neural networks

At the heart of much modern CAD software is a type of machine learning technique known as deep (learning) neural networks. Since 2012, when impressively accurate image recognition was achieved by a special configuration of deep neural networks known as AlexNet, this approach has become the default for all tasks involving image processing and analyzing.

Compared to more traditional techniques such as linear and logistic regression, or decision trees, neural networks are distinguished by multiple layers of calculations and a large number of dimensions. This complexity increases their opacity: the difficulty of interpretability for scientists keen to define, and ideally explain, the nuts and bolts of the final decision process. Any perceived mystery ascribed to AI derives from that opacity.

A detailed explanation of how deep neural networks function can be found in Annex 1.

What can neural networks predict?

In medical imaging, there are three types of tasks to which a deep neural network can be applied: classification, detection and segmentation (see Box 1).[9]

Box 1: Different use categories of AI in medical diagnostics

1) Classification

   This is where the AI has a pre-defined set of categories into which it must classify the image, including the presence or absence of abnormality, or the type of abnormality, or whether a patient will respond to treatment.

   If the prediction is a continuous value, such as when predicting antibody titres, or laboratory values, this is termed regression.

2) Detection

   This is the detection, and prediction, of locations of points of interest on images, where output is presented in the form of points, regions, or bounding boxes.

3) Segmentation

   This is the delineation (i.e., outlining) of abnormalities in structures of interest at the level of the pixel. These can be used to map the surface of points of interest in the body when planning for virtual surgery, for example, or radiation therapy.

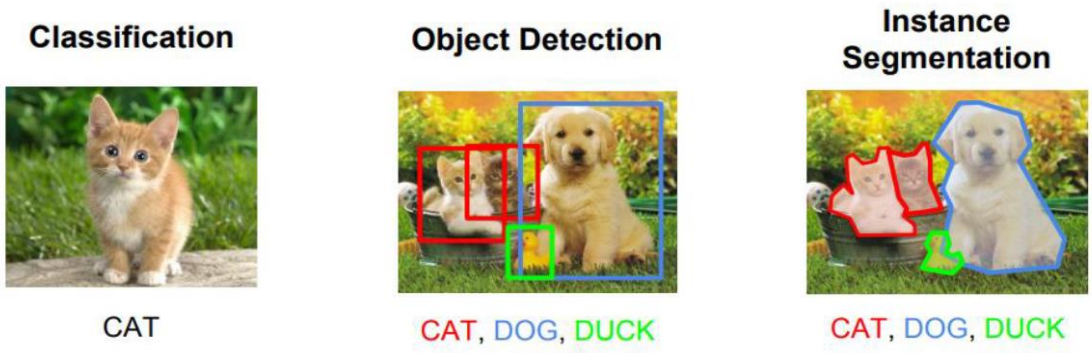


Image taken from the internet

Most commercial CAD products for TB can perform **classification** (such as whether TB-related abnormalities are present or absent) and **detection** (providing a heatmap indicating location of abnormalities). Please see for Section 1.4 for more detail on understanding CAD outputs.

Section 1.3 CAD Product Landscape

A recent landscape review led by the Stop TB Partnership and the Foundation for Innovative New Diagnostics (FIND) identified a total of 28 CAD developers and 12 TB-specific products already on the market (as of March 2021).[10] The results are published on the www.ai4hlth.org website, which contains detailed and regularly updated information on available CAD products for TB. As of publication, the TB-specific CAD products with a CE-mark are: AXIR from RadiSen (South Korea), CAD4TB from Delft Imaging (Netherlands), InferRead DR Chest from Infervision (China), JVIEWER-X from JLK (South Korea), Lunit INSIGHTCXR from Lunit (South Korea), and qXR from Qure.ai (India)[10,11] (Figure 1).

Figure 1 Commercial AI products for TB available on www.ai4hlth.org

The landscape of CAD products for TB is rapidly growing, and innovative new products are expected to either reach the market or receive certification later in 2021. The www.ai4hlth.org website will continue to be the most up-to-date resource.

Common Product Characteristics

As the CAD market for TB expands, it is possible to identify some characteristics common to all products. Together, these offer a snapshot of how CAD is operationalized (see Figure 2).

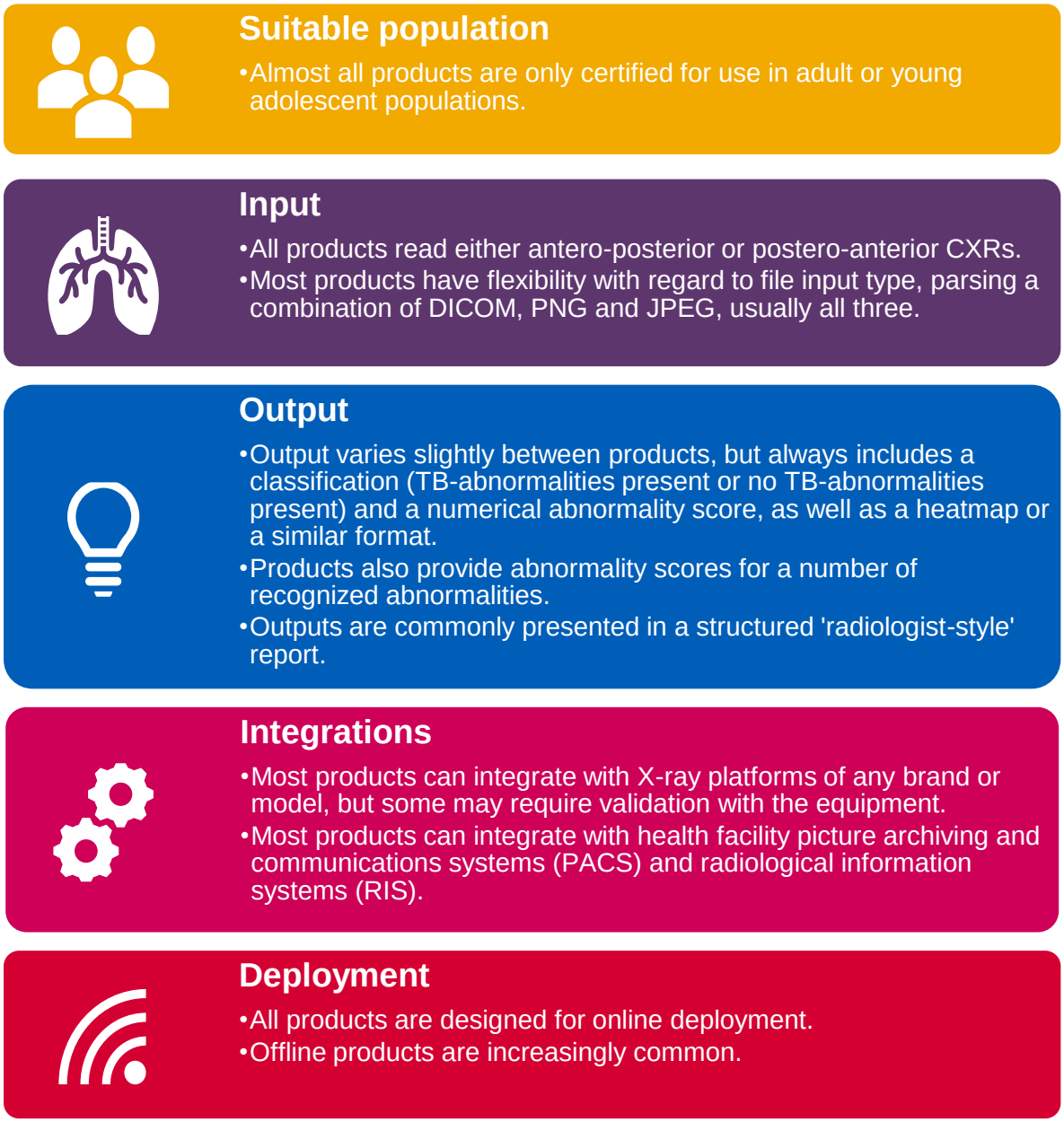


Figure 2 Common characteristics of CAD products.

Input

Once properly installed, input X-ray images pass automatically from the X-ray system to the computer where the CAD product is installed. CAD products are designed to read CXR images in common image file formats, including DICOM (Digital Imaging and Communications in Medicine), JPEG, and PNG. Almost all products can read either antero-posterior (AP) or postero-anterior (PA) CXRs.

Output

CAD software analyzes input images to produce a series of interpretable outputs. As a minimum, CAD output consists of an abnormality heatmap, a number (the abnormality score) and/or dichotomous decision: “TB-related abnormalities present or absent”. That number

conveys the likelihood that the image being analyzed contains abnormalities associated with TB. Output may be structured in formats familiar to clinicians, such as radiology-style reports, and can be customized to suit the diagnostic processes at the implementation site.

CAD output is discussed in more detail in Section 1.4.

Integrations

Most CAD products are X-ray system vendor neutral. The CAD may also be integrated with an archiving system for the automatic storage of CAD outputs. In fact, most CAD products support integration with a picture archiving and communications system (PACS) and a radiological information system (RIS).

Deployment

Online (cloud-based) CAD products are the most common. With these, the user needs the internet for the transmission of a digital CXR to a dedicated server, where the AI performs the analysis before sending the result back to the user's computer. The server can be a cloud or physical server that may or may not be located in the same country as the user. CAD products can also be deployed as an offline product, and this mode is increasingly becoming available for settings with an unreliable or absent internet connection.

For a summary of the specifications of the current available products, please refer to Table 1 (for those already CE-marked), and Table 2 (for those pending certification), both derived from www.ai4hlth.org.

Table 1. Summary of product characteristics for CAD software on the market with CE mark

Developer	**Delft Imaging Systems**	**Infervision**	**JLK**	**Lunit**	**Qure.ai**	**RadiSen**
Product	CAD4TB	InferRead DR Chest	JLD-02K (JVIEWER-X)	Lunit INSIGHT CXR	qXR	AXIR
Version	7	1.0	1.0	3.1.0.0	3.0	1.1.2.2
Based in	The Netherlands	China	South Korea	South Korea	India	South Korea
CE Mark[2]	✓ (for version 6)	✓	✓	✓	✓	✓
Target population (age range) [3]	4+	16+	10+	14+	6+	16+
Input	PA CXR	AP/PA CXR	AP/PA	AP/PA	AP/PA	PA CXR
DICOM	✓	✓	✓	✓	✓	✓
JPEG	✓	✓	✓		✓	
PNG	✓	✓	✓		✓	
Output						
Score for TB	✓	✓	✓	✓	✓	✓
Heatmap	✓	✓	✓	✓	✓	✓
Binary 'TB/ Not TB'	✓	✓	✓	✓	✓	✓
Deployment options	Online and offline	Online and offline	Online and offline	Online and offline	Online and offline	Offline
Developer-recommended threshold score?	✓	×	✓	✓	✓	✓

Note: AP = antero-posterior, PA = postero-anterior, PACS = picture archiving and communication system, CXR = chest X-ray

Data extracted from www.ai4hlth.org on 14 April 2021. At time of publication this data was correct, regular updates are provided, and updated information is available first on ai4hlth.org.

[2] CE mark (*Conformité Européenne*) indicating a product's conformity with European Economic Area directives or standards.
[3] Manufacturer-designated age range. The World Health Organization only approves the use of CAD software for individuals aged 15+.

Table 2. Summary of product characteristics for CAD software on the market awaiting CE mark

Developer	**Deeptek**	**Epcon**	**JF Healthcare**
Product	GENKI	Xray AME	JF-CXR-1
Version	2.0	1.0	3.0
Based in	India	Belgium	China
CE Mark?	Pending	Pending	Pending
Target population and setting	14+	18+	15+
Input	AP/PA CXR	AP/PA CXR	PA CXR
DICOM	✓	✓	✓
JPEG	×	✓	×
PNG	✓	✓	×
Output			
Score for TB	✓	✓	✓
Heatmap	✓	✓	✓
Binary ‘TB/ Not TB’	✓	✓	×
Deployment options	Online and offline	Online and offline	Online and offline
Developer-recommended threshold score?	×	✓	✓

Note: AP = antero-posterior, PA = postero-anterior, PACS = Picture archiving and communication system, CXR = chest X-ray

Data extracted from www.ai4hlth.org on 14 April 2021. At time of publication this data was correct, regular updates are provided, and updated information is available first on ai4hlth.org.

Add-on Features

In response to end-user feedback, manufacturers adapted their CAD products to improve performance and expand functionality.

Examples of some additional features include:

1. **Generating results in standard radiology report formats:** Updates create a more user-friendly and interpretable output for radiologists. Reports may be generated using customizable output fields.
2. **Providing real-time data dashboards:** Software packages that accompany CADs increasingly provide a user-friendly visual overview of people who have been screened, showing demographic and clinical data.
3. **Ability to digitize analogue CXRs:** Some solutions on the market can digitize CXRs for optimal reading. Radiology technicians follow a step-by-step guide to place the analogue CXR on a light box, and then position the image correctly within the margins indicated on the app. As soon as the photo is taken, the application digitizes the analogue CXR and links it to the CAD system.
4. **Ability to detect an expanded range of diseases and abnormalities:** Increasingly, products can function far more like a human radiologist than did the simple TB-detecting tools from which they have evolved. Some TB-CAD software products can classify common CXR abnormalities, such as calcification, cardiomegaly, mass, nodule, and pleural effusion, as well as bone and heart abnormalities. Although this guide primarily considers CAD tools for TB, multi-disease CADs are also available. This kind of development was exemplified by the adaptation in 2020 of some CADs to enable them to detect COVID-19 infections. However, there is a lack of independent evaluation data on the performance of CAD for differential diagnosis and how accurately it localizes abnormalities. Which other non-TB abnormalities can be reported on – according to the manufacturers of various CAD products – is outlined in Table 3 (from data at www.ai4hlth.org accessed 14 April, 2021).

Table 3. TB and non-TB abnormalities that current CAD software products report on, independent of score for TB.

	Calcification	Cardiomegaly	Cavity	Consolidation	Fibrosis	Lymphadenopathy	Mass	Nodule	Opacity	Pleural effusion	Pneumothorax
AXIR			✓				✓	✓			✓
CAD4TB*											
Chest Eye	✓			✓	✓	✓	✓	✓	✓	✓	✓
GENKI	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
InferRead DR Chest	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
JF-CXR								✓			
JLD-02K		✓		✓	✓		✓	✓		✓	✓
Lunit INSIGHT CXR	✓	✓		✓	✓			✓		✓	✓
qXR	✓	✓	✓	✓	✓			✓	✓	✓	✓
Xray AME*											

*CAD4TB and Xray AME may also consider some of the listed abnormalities in their score for TB but do not give a separate score for each abnormality.

For the full list of abnormalities each TB CAD software can report on, please see www.ai4hlth.org

Disclaimer: there is a lack of independent evaluation data on the performance of CAD for differential diagnosis and how accurately it localizes abnormalities.

Section 1.4. CAD Output and How to Understand It

As discussed previously, most CAD software can perform **classification** (such as abnormalities suggestive of TB being present or not) and **detection** (displaying a heatmap). It is important to understand what an output generated by CAD software means – and what it does not mean – when using it to inform important medical decision-making. This section presents an overview of the TB-CAD software prediction, and how to understand it.

CAD Output

Output reports and interfaces differ from one CAD software product to another, but all will generally provide:

1) A heatmap indicating the area of the chest where an abnormality is present ("detection");
2) a numerical abnormality score, ranging from zero to one (or 0-100), for the abnormalities or diseases it can detect, including TB and other lung abnormalities ("classification");
3) a dichotomized (binary) classification of the abnormalities a CAD software can detect (abnormalities suggestive of TB being present or not) based on the abnormality score described above, which is modifiable;
4) An automatically generated standard radiology report (some software only).

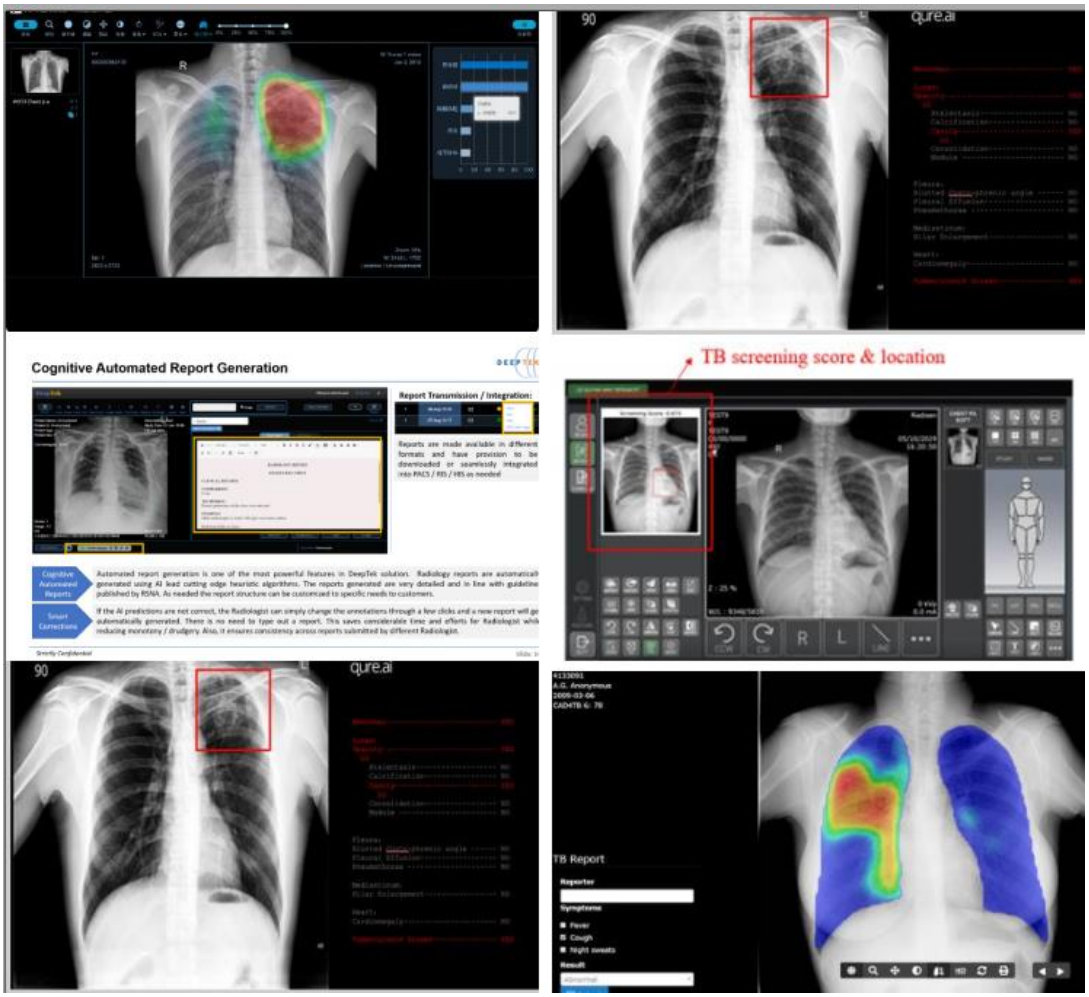


Figure 3 Example Outputs from commercial TB-CAD software s according to www.ai4hlth.org.

How to Interpret an Abnormality Score

TB-CADs are image classification algorithms because they read a CXR for abnormalities to assign a classification of TB-suggestive abnormalities being present or not. This classification is based on a score of between zero and one (or 0-100) that represents the **likelihood** of TB being present in a particular CXR. The output of CAD is therefore continuous: the higher the score, the higher the likelihood that the model assigns the image to the "TB-suggestive abnormalities present" category.

The abnormality score should not be considered a probability. It is important to note that **abnormality scores are not necessarily linearly related to the objective probability of the CXR containing signs of TB;** nor are these scores standardized in the same way across different CAD software products. TB likelihood is also independent of disease prevalence. Thus, for example:

- An image with a score of 0.4 is not necessarily twice as likely to contain TB as an image with a score of 0.2.

- A score of 0.5 from one CAD algorithm does not necessarily mean the same as a score of 0.5 from another CAD algorithm.

Dichotomization

The abnormality score, described above, is a continuous numerical output that can be translated into a binary classification by **selecting a cut-off point** on the abnormality score (between zero and one), above which the "abnormalities suggestive of TB are present" classification is assigned. A CXR with an abnormality score below the cut-off would be assigned the "abnormalities suggestive of TB are absent" classification. This score is variously referred to as the **threshold score, operating point, "cut-off" or "cut point".** Because different commercial CAD software products have been developed independently, the underlying neural networks are constructed differently and hence the distributions of abnormality scores are not the same. Similarly, different versions of the same software can be constructed differently, and this too will result in different distributions of abnormalities scores. As a result, **there is no universal threshold score across CAD software and across software versions from the same supplier.**

CAD abnormality score distribution also differs in different populations, depending on disease prevalence, intervention setting and use case. This means that even for a given software product, different populations may warrant different thresholds. For example, a comparison of CAD4TB performance in a study in Nepal and a study in Cameroon showed that a threshold of 0.63 in the Nepal study yielded a sensitivity of 95%, whereas in the Cameroon study a lower threshold of 0.48 was required to achieve the same sensitivity.[12] The selection of the operating point is thus in part dictated by the local TB prevalence, and even within a single country this might vary from region to region, or from urban to rural setting, and so forth.

Some manufacturers recommend a default threshold score based on their general experience with the software, but this may not be the most appropriate for a given context or the goals of a given programme. One way to select a threshold score is by conducting **on-site calibration studies**. Chapter 5 explains how to calibrate and select a threshold score.

Section 1.5. Validation of Commercial CAD Software for TB Screening and Triage

Since the inner workings of CAD software are challenging to understand for both general audiences and developers, confidence in the ability of CAD software to detect TB should be earned by comprehensive and unbiased software evaluations that measure different performance indicators on real-world datasets. This section discusses what has been done to validate CAD so far, including the populations and use cases in which validation studies have been performed and the recorded performance of CAD thus far. We conclude by discussing the gaps in the CAD literature, particularly around key populations.

Box 2 Evaluation of CAD performance by WHO

WHO reviewed the accuracy of three CAD software programmes in order to generate its guidelines on screening and triage of TB. These were CAD4TB (version 6), from Delft Imaging; Lunit Insight CXR, from Lunit; and qXR (version 2), from Qure.ai. Each was assessed independently by three different groups, using CXR libraries unavailable for CAD software development or training. The three evaluations were conducted without the involvement of the manufacturers. The diagnostic accuracy and the overall performance of the CAD software were found to be **similar** to interpretation of digital CXR by a human reader in their ability to identify bacteriologically confirmed TB, in both the screening and triage contexts.

Below is the range of sensitivity and specificity of the three CAD software products, and human readers, interpreting digital chest radiographs for detection of bacteriologically confirmed TB in a range of population and settings.[4] (The CAD technologies were set to a threshold that achieved a 90% sensitivity as per the WHO target product profile for triage test, and the matching specificities were evaluated and compared.)

Type of case and type of reader	Accuracy estimate range	
	Sensitivity	Specificity
WHO target product profile	> 0.90	> 0.70
Screening use case		
CAD software	0.90–0.92	0.23–0.66
CXR with human reader	0.82–0.93	0.14–0.63
Triage use case		
CAD software	0.90–0.91	0.25–0.79
CXR with human reader	0.89–0.96	0.36–0.63

CAD: computer-aided detection; CXR: chest X-ray.

Unlike traditional diagnostic tests, which take years to produce and update, the performance of AI improves extremely rapidly. New software is set to emerge in the near future and updated software versions are launched almost annually. The CAD software evaluated by WHO for the guideline update (Box 2) only included three commercial software products and all have been already replaced by new software versions.[4] Two additional commercial CAD software products, InferRead DR Chest and JF-CXR, are also featured in independent journal publications on diagnostic performance[13].

[4] Taken from 2021 update on WHO consolidated guidelines on Tuberculosis screening.

CAD4TB is the most extensively evaluated software, but most of the published evidence involves authors linked to the manufacturer,[5] and are therefore omitted from the summary below. There is a lack of data on the accuracy of CAD when classifying non-TB abnormalities and on the accuracy of CAD at locating abnormalities.

The performance of a CAD software product can be measured: 1) globally, using the continuous output, and 2) at a specific operating point, using the binary output. This document focuses on summarizing the published performance data on classifying the presence or absence of TB-related abnormalities using both measures, with microbiological evidence as the reference standard.

Box 3 Software version

When reading CAD software evaluations, it is essential to take note of the software version. Though the name of the software is unchanged, the underlying AI model and its performance can differ between versions, with newer versions reportedly improving significantly on older ones.[14] Publications reporting on older versions of CAD software are therefore of no relevance for decision making, because newer versions have improved performance.

Receiver Operating Characteristic (ROC) Curves

The overall accuracy of a CAD software product is measured over the complete range of abnormality scores (0-1 for most software, 0-100 for CAD4TB). ROC curves plot the CAD's true positive rate (sensitivity) against the false positive rate (1-specificity). The **area under the ROC curve (AUC)**, between zero and one, is directly related to the overall accuracy of a CAD software, with 0.5 representing the accuracy of a random guess.

Table 4 is a summary of AUCs reported in papers identified as of March 2021 on PubMed (previous software versions are marked in grey), excluding those with authors linked to the CAD developers or suppliers. Due to the limitations of radiological assessment (inter-and intra-reader variability), we also only included papers using bacteriological evidence as the reference standard though this is not without limitation.

The reported AUCs of the latest versions of the 5 commercial CAD software are between 0.82 and 0.91. In general, accuracy is therefore high since an AUC of 1 would represent a perfect diagnostic test.

[5] CAD4TB is developed by Radboud University, Thirona and Delft Imaging

Table 4. Reported AUCs in the published research evaluating CAD performance against a microbiological reference standard

Software	**Version**	**Publication**	**Study Country**	**Study Population** (years old)	**AUC**
CAD4TB	7	Qin 2021[13]	Bangladesh	15+ years old, triage use case, symptomatic	0.90 (0.90-0.91)
	6	Qin 2019[12]	Cameroon	15+ years old, triage use case, some asymptomatic	0.87 (0.84-0.91)
			Nepal	15+ years old, triage use case, symptomatic	0.89 (0.79-1)
	3.07	Rahman 2017[15]	Bangladesh	15+ years old, triage use case, symptomatic	0.74 (0.73-0.75)
qXR	3	Qin 2021[13]	Bangladesh	15+ years old, triage use case, symptomatic	0.91 (0.90-0.91)
	2	Qin 2019[12]	Cameroon	15+ years old, triage use case, some asymptomatic	0.91 (0.88-0.94)
			Nepal	15+ years old, triage use case, symptomatic	0.93 (0.85-1)
		Nash 2020[16]	India	18+ years old, triage use case, symptomatic	0.81 (0.78-0.84)
Lunit INSIGHT CXR	4.9.0	Qin 2021[13]	Bangladesh	15+ years old, triage use case, symptomatic	0.89 (0.88-0.89)
	4.7.2	Qin 2019[12]	Cameroon	15+ years old, triage use case, some asymptomatic	0.91 (0.88-0.94)
			Nepal	15+ years old, triage use case, symptomatic	0.93 (0.86-1)
InferRead DR Chest	2	Qin 2021[13]	Bangladesh	15+ years old, triage use case, symptomatic	0.85 (0.84-0.86)
JF CXR-1	2	Qin 2021[13]	Bangladesh	15+ years old, triage use case, symptomatic	0.85 (0.84-0.85)

Studies using versions of software that are now out-dated are marked in grey.

Precision Recall Curve (PRC)

Another analysis that can help implementers to review the performance of different software is the precision recall curve (PRC). The PRC plots precision, known as positive predictive value (PPV), against sensitivity over the continuous range of threshold scores of a software product. The higher the area under the PRC (PRAUC), the more accurately the CAD software identifies TB in the study setting and population. Implementers may use the PRC to compare between CAD products and inform product selection. Research shows that PRC curves offer a better measure of product accuracy than the ROC in "unbalanced" datasets (or populations), such as in TB target populations where the number of people with and without TB is not equal.[17]

Intervention populations invariably produce an unbalanced TB dataset. Given that in almost all real settings TB prevalence is well below 50%, PRC is the better measure to use when comparing the performance of different CAD software products. With unbalanced datasets, it is often easier to use PRC to visualize differences between the performance of different AI software products. Figure 4 shows an example ROC and PRC curve where TB prevalence is 15.4%[13]. The different curves largely overlap in the ROC plot and it is therefore difficult to identify the difference in performance of the CAD software. But in the PRC plot (right), the difference in the performance of the CAD software is more salient.

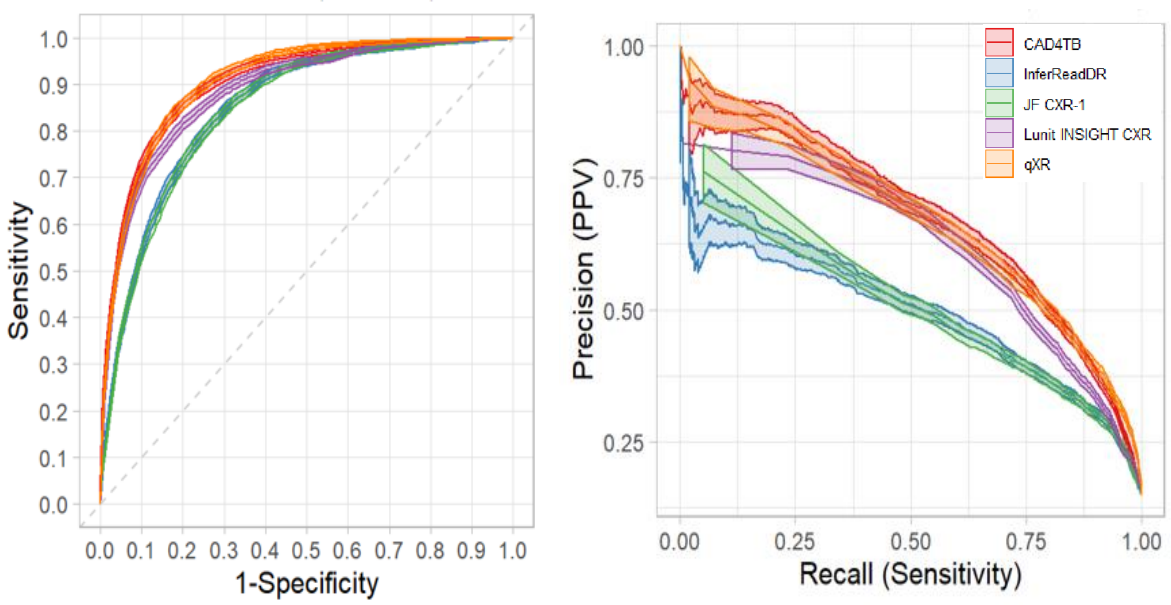


Figure 4 ROC curve (left) and PRC curve (right) from a site where TB prevalence is 15.4%.[13]

Neither ROC or PRC should be used for threshold score selection as neither can give indications of sensitivity and specificity for specific threshold scores.

Sidebar: ROC and PRC: why are they useful and why use both?

The sensitivity and specificity of CAD tools are completely elastic and dependent on the threshold selected. Therefore, in CAD literature, Receiver Operating Characteristic (ROC) are Precision Recall Curve (PRC) are commonly used to measure the overall performance of CAD products across the entire range of threshold scores.

The area under each curve (AUC) provides a gateway for harnessing the existing CAD literature to learn:

- How overall performance varies between CAD products;
- How different versions of the same CAD product compare;
- How the performance of a given CAD product will vary in key populations, such as persons living with HIV (PLHIV); and
- If CAD performance differs depending on patient source (active case finding, self-referral, referral from facility).

ROC: each point on an ROC graph represents the CAD's sensitivity and 1-specificity at a particular threshold score. The graph itself is not easily interpretable, but the AUC provides an understandable metric of CAD performance (AUC of 1 indicates perfect performance, though this has yet to be seen).
PRC: is similar to ROC but is often seen in studies using data with low TB prevalence. PRC can magnify the differences in CAD performance (as described in the main text).
A CAD product or version with a higher AUC will generally outperform those with lower AUCs.

Comparison against the Target Product Profile of a Triage Tool

Both ROC and PRC curves measure the overall performance of the CAD software; however, depending on the needs and aims of the programme, certain parts of the curves will be of much greater relevance than the entire curve. For example, when trying to maximize case detection, high sensitivity is more important than high specificity. When trying to maximize the efficiency of the algorithm and preserve costly confirmatory test cartridges, specificity may be prioritized even during screening or triage.

In 2014, WHO released a report summarizing the desirable characteristics, or target product profiles (TPPs), of triage tests for detecting TB disease.[18] The report highlighted that the minimum requirements for a triage test to detect pulmonary TB disease – or rule it out – would be an overall sensitivity of 90% and a specificity of 70%. One paper shows that three CAD software packages (qXR, CAD4TB, and Lunit INSIGHT CXR) came close to those targets (Table 5).

Table 5. Comparing CAD performance against the WHO Target Product Profile (TPP) using a microbiological reference standard

Publication, Country	CAD software (version)	Threshold Score	Sensitivity	Specificity
Threshold score selected closest to 90% sensitivity				
Qin 2021, Bangladesh [13]	CAD4TB (v7)	62	90.0% (89.0-91.0%)	72.9% (72.3-73.5%)
	InferRead DR Chest (v2)	0.34	90.3% (89.3-91.3%)	62.1% (61.4-62.7%)
	JF CXR-1 (v2)	0.92	90.4% (89.4-91.3%)	61.1% (60.4-61.8%)
	Lunit INSIGHT CXR (v4.9.0)	0.6	90.1% (89.0-91.0%)	67.2% (66.6-67.9%)
	qXR (v3)	0.6	90.2% (89.2-91.1%)	74.3% (73.3-74.9%)
Nash 2020, India[16]	qXR (v2)		*Exact value not provided*	42% (30-57%)
Threshold score selected closest to 70% specificity				
	CAD4TB (v7)	69	91.5% (90.5-92.4%	70.0% (69.4-70.6%)

Qin 2021, Bangladesh[13]	InferRead DR Chest (v2)	0.47	84.0% (82.8-85.2%)	70.6% (69.9-71.2%)
	JF CXR-1 (v2)	0.98	85.0% (83.8-86.2%)	68.8% (68.2-69.5%)
	Lunit INSIGHT CXR (v4.9.0)	0.67	88.8% (87.7-89.8%)	70.1% (69.4-70.7%)
	qXR (v3)	0.51	92.6% (91.7-93.4%)	70.3% (69.6-70.9%)
Nash 2020, India[16]	qXR (v2)		77% (72-82%)	*Exact value not provided*

Performance in Key Populations

Though many of the above studies conclude that CAD software products perform well in the general population, their performance in TB key populations needs more evaluation to ensure CAD will help close, not widen, healthcare disparities. This is particularly relevant where the group of interest is unable to produce a quality sputum sample for microbiological confirmation of TB as the reference standard. Sub-analyses in key populations are notably absent in CAD literature. There is a lack of independent evaluation data on **children**, people with a co-morbidity such as **diabetes**, and **pregnant women**. There is also a lack of data on the ability of CAD to differentiate **latent TB** from active TB. Three papers on earlier versions of CAD4TB demonstrated that the CAD product performs worse in **HIV positive** individuals.[19,20] Implementers could consider monitoring and reporting the performance of CAD in their target population, especially in key sub-populations, to contribute to this growing global body of literature.

Future development

The current literature is of mixed quality. Perhaps unsurprisingly, it includes somewhat contradictory assessments with notable conflicts of interest. New software, and new software versions, are being developed at pace, that are yet to be evaluated independently. One of the primary goals of the Digital Health Technology Hub of the Stop TB Partnership is to develop an independent online platform for semi-automated evaluation of CAD software, using the Stop TB archive of CXR images, which are all linked to a bacteriological reference standard. This will help implementers understand the performance of the latest versions of CAD software.

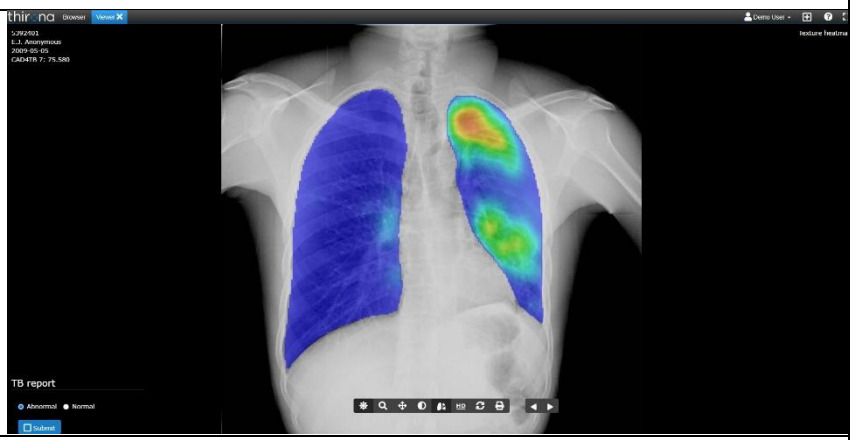
Chapter 2 CAD Software and Implementation Considerations

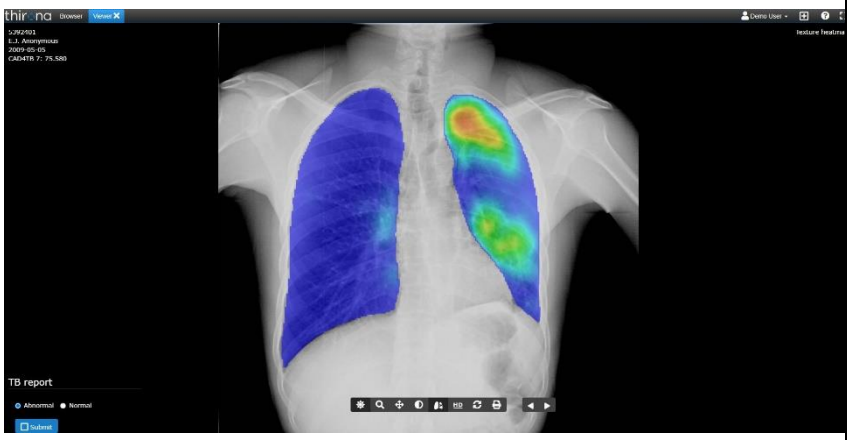
When selecting a CAD supplier (Section 1.5), performance and price are fundamental criteria, but there are other vital considerations, including the availability of internet connectivity, the portability (of hardware), compatibility with X-ray systems, and integration with any existing RIS or PACS system. This chapter begins by introducing the CAD tools in Stop TB Partnership's Global Drug Facility (GDF) catalog in terms of internet connectivity, software and hardware requirements, server and storage, integration with CXR systems and PACS, and price. The following chapter looks in more detail at integration of the CAD products with the ultra-portable X-ray systems in the GDF catalog (Chapter 3). That chapter then runs through several crucial topics relevant to selection of CAD software, accompanied by Annex 2, which is a template of specifications for a procurement tender (this should be customized to meet the needs of a specific programme).

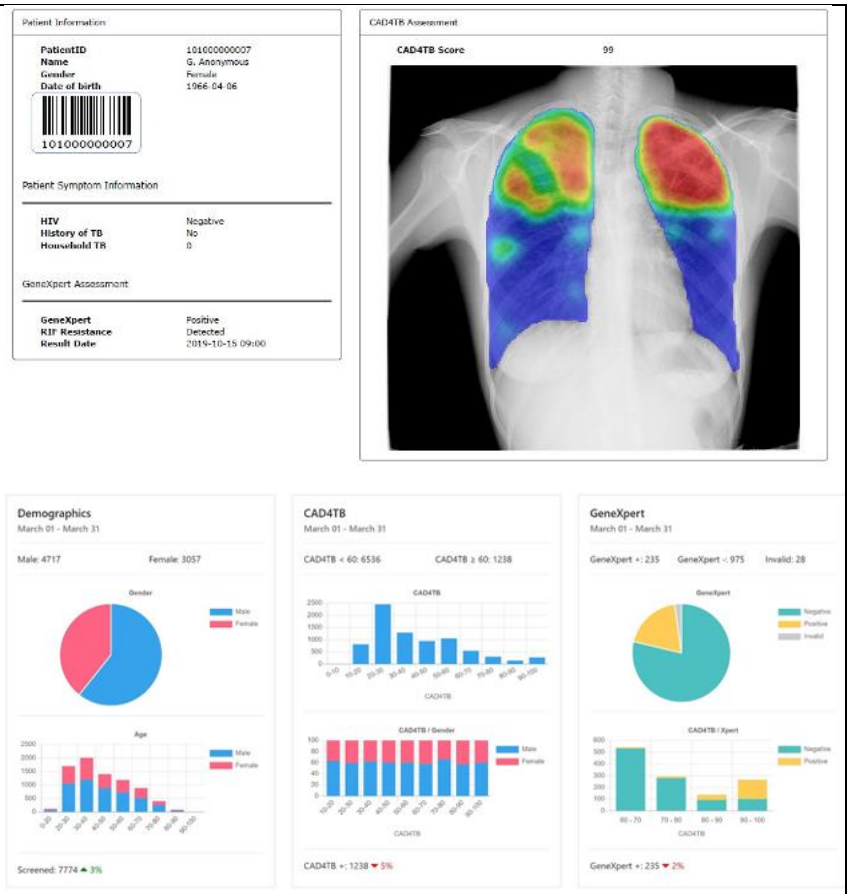
Sidebar: The performance of CAD4TB and InferRead DR Chest

Recap Section 1.5: The WHO recommendation on the use of CAD technology is agnostic to the brand but is based purely on available performance data of three CAD products that had received a CE mark by January 2020 (Box 2). CAD4TB was included in the WHO evidence review, but not InferRead DR Chest, for which no peer-reviewed manuscripts were available at the time. Only one publication evaluates CAD4TB alongside InferRead DR Chest (on 23,954 chest X-rays from Bangladesh). In this population, with relatively high TB prevalence (15.3%), both products significantly outperformed the Bangladeshi radiologists hired through the project and could save significant numbers of confirmatory tests while maintaining high sensitivity. CAD4TB (AUC = 0.9 [0.90-0.91]) showed a slightly better overall performance than InferRead DR Chest (AUC = 0.85 [0.84-0.86]). However, in view of the paucity of independent data on performance, further research is awaited, using different populations and in a variety of settings.

CAD4TB by Delft Imaging (the Netherlands)

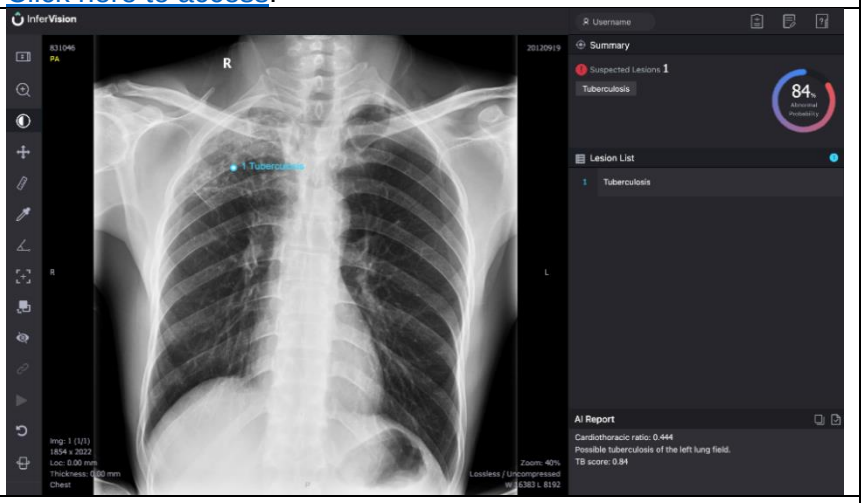
Supplier	Delft Imaging
Supplier HQ	's-Hertogenbosch, The Netherlands
Version	7
Picture of the software interface / output	
Certification	CE 0344
Population Group/Appropriate Population	Adults & Children: Regulatory approval for adults and children aged 4 years and above.

Target Setting	Outreach and mobile health services, primary healthcare facilities, general hospitals (above primary level), occupational health programmes, teleradiology companies, government/public sector, e.g. national TB programme, private sector.
Current Market	CAD4TB is in use in over 40 countries worldwide. A complete list can be found on the website: https://www.delft.care
Input	Can be used to read images from any kind of digital CXR machine. Chest X-ray image format: DICOM, PNG, JPEG. By using an app (SNAP4CAD), analogue X-ray images can be used as well. Chest X-ray type: PA (Posterior-Anterior) CXR (from stationary, portable, and ultra-portable X-ray systems).
Output	The CAD4TB results consist of: ● abnormality score for TB and ● heat map ● binary classification “TB” or “Not TB”  The output format is configurable, making it fully compatible with existing infrastructure, such as PACS systems. With the new CAD4TB platform, a full report with screening results is available, alongside an advanced management dashboard to monitor screening progress.

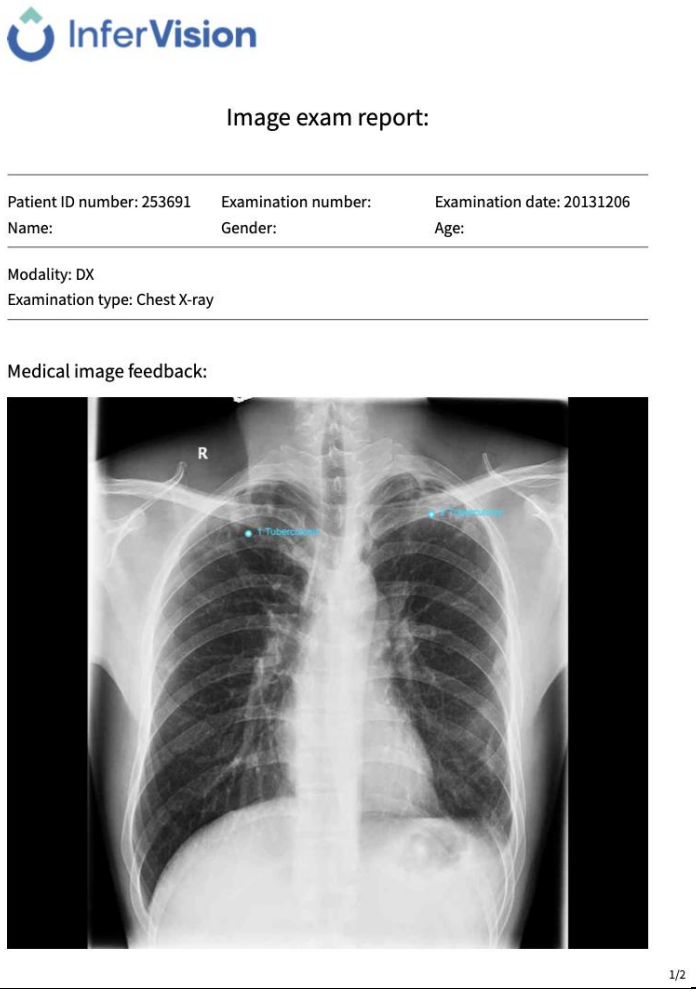
	
Deployment	Online and offline.
Hardware	CAD4TB comes as a complete product and is installed on a mini-computer called CAD4TBbox.
X-ray system validation	Because of the variety of X-ray systems (more than 30 different machines), and populations, in which the software has been validated (validation is not mandatory but may be performed if desired).
Software	CAD4TB 7 runs on Linux. Currently, Ubuntu LTS 16.04 or newer is preferred.
Server	All leading cloud computing providers are supported. In-country or on-premise servers are available upon request.
Processing Time	Less than 20 seconds for the CAD4TBbox. Cloud results processing time dependent on internet connectivity.
Data Sharing & Privacy	
Server location (for online mode)	All leading cloud computing providers are supported – having multiple data centers around the world. In country or on-premise servers are also available upon request.
Data shared with manufacturer?	No. As a company headquartered in the Netherlands, the developer follows the General Data Protection Regulation (GDPR) of the European Union. Each customer therefore receives a Data Processing Agreement that clearly explains how their data is processed and used. The developer does not use the data for any other purpose than to provide the CAD4TB result for the customer, unless given explicit written permission. Any

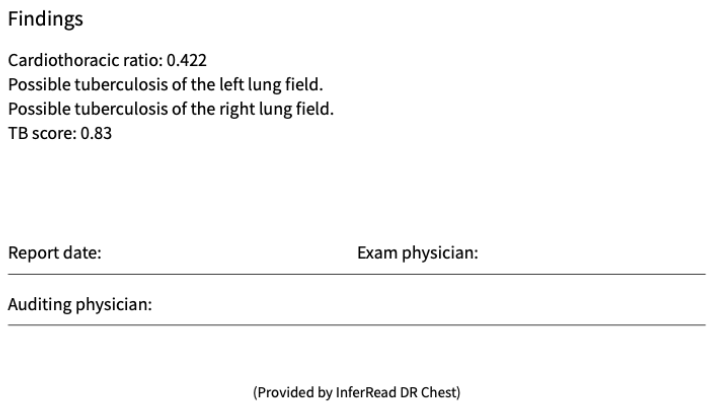
	data processed by CAD4TB remains the property of the customer.
De-identification (option to de-identify?)	Yes. Data is de-identified before it is sent to the server in order to make sure no personal information is sent over the internet compliance with privacy regulations is secured.
Software Updates	
Frequency	Annual
Software Development	
Method (used to develop software)	Supervised deep learning (CNN, RNN) plus manual feature engineering.
Training	The software was trained on 1,000,000 X-rays from several countries and continents.

InferRead DR Chest by InferVision (China)

Supplier	Infervision Medical Technology Co., Ltd.
Supplier HQ	Beijing, China
Version	1.0.0.0
User manual	Click here to access.
Picture of the software interface / output	
Certification	CE 2797
Intended Age Group	16+ years (CE approved); manufacturer recommends use in 12+ years.
Target Setting	Primary health centers, general hospital (above primary level), teleradiology companies, government/public sector e.g. national TB programme, private sector.
Current Market	As of May 2021, Infervision has service-sites covering many parts of China, and has expanded its global reach across the Asia-Pacific region, North America and Europe, with a presence in 20+ countries worldwide.
Input	Can be used to read images from any kind of chest X-ray system. Chest X-ray image format: JPEG, PNG, DICOM. Chest X-ray type: Posterior-anterior chest X-ray, anterior-posterior chest X-ray.

	Other requirements: shall be specified according to local circumstances.

Output	Structured report includes:
	• Heat map / Region of Interest,
	• Dichotomous output indicating the presence or absence of the following abnormalities:
	  ○ TB,
	  ○ Nodule, fracture, pneumothorax, pleural effusion, infection (pneumonia) and aortic calcification (can be turned off upon request),
	• Probability score for TB,
	• Probability score for each abnormality, location of each abnormality.
	 
	InferVision
	Image exam report:
	Patient ID number: 253691 Examination number: Examination date: 20131206
	Name: Gender: Age:
	Modality: DX
	Examination type: Chest X-ray
	Medical image feedback:
	R
	1/2

	
Deployment	Online & Offline
Hardware	online mode: CPU: Intel Core i3 and above; Memory: Above 4GB RAM Offline mode: CPU = Intel i7 6,850K processor and above; GPU = NVIDIA GeForce 1,080 and above or V100 and above; RAM = DDR4 is recommended with a capacity of at least 16GB; solid state system hard disks with capacity of at least 120GB; high-speed mechanical hard disk with a capacity of at least 1TB and storage disk rotation speed of 7,200 rpm.
X-ray system Validation	Validation is recommended if the software is installed on the X-ray system for the first time. The data transmission needs to be tested to ensure that the workflow can operate appropriately.
Software	Computer requirements: 1. Operating system: Windows XP and above. 2. Browser：Chrome 49.0 and above. Server requirements: 1. Operating System：Ubuntu 18.04 LTS and above. 2. Browser：Chrome 49.0 and above.
Server	Requirements for server hardware: 1. CPU：4-core processor and above (such as Intel i7 6850K). 2. GPU：NVIDIA GeForce 1080 and above, or V100 and above. 3. Memory：DDR4 is recommended, with a capacity of at least 16GB. 4. Hard disk: For system disk, choose solid state hard disks with capacity of at least 120GB; a high-speed mechanical hard disk (rotation speed of 7200 rpm) with a capacity of at least 3TB.

	5. Network card： 1000M PCI-E network card.
Integration	It is possible to integrate the software with the client's legacy Picture Archiving and Communication System (PACS).
Processing Time	Using the minimum client configuration, and under gigabit broadband, it takes less than 5 seconds to process 1 DICOM image.
Data Sharing & Privacy	
Server location (for online mode)	Located worldwide (google cloud) and/or a local or national server can be set up if required.
Data shared with manufacturer?	No.
De-identification (option to de-identify?)	De-identification option can be provided if required by customer.
Software Development	
Method	Supervised deep learning (CNN, RNN).
Training	Not disclosed.
Reference Standard	Culture, smear, and human reader.

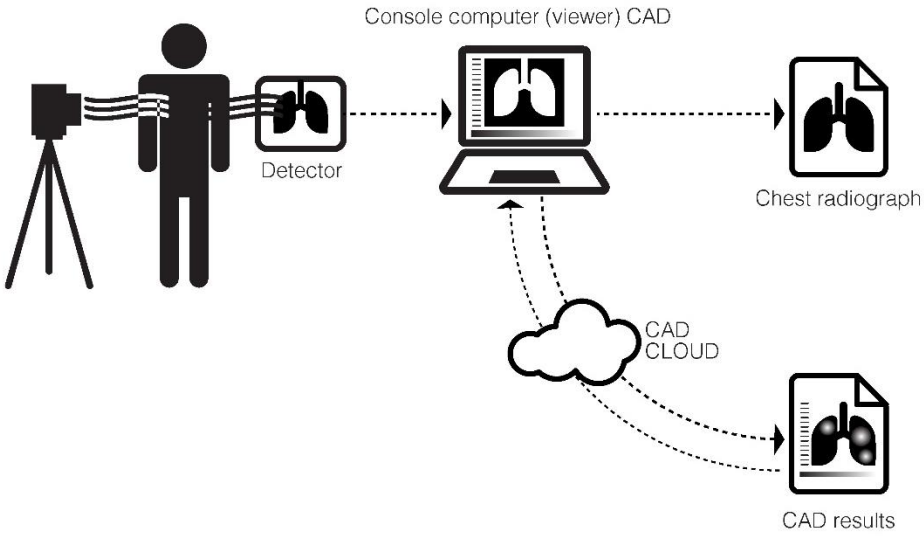
Section 2.1 Internet Connectivity and Hardware Requirement

We begin by discussing the internet connectivity of CAD, because whether CAD software is used online, offline, or in a hybrid of the two plays a fundamental role in determining the hardware and software requirements of CAD in the field. Understanding the configurations of CAD in each mode therefore paves the way for a seamless integration of CAD with existing systems.

Online (Cloud) mode

Cloud processing is the most common method of deployment and is offered by both CAD software suppliers (Delft Imaging Systems and InferVision). The X-ray system workstation / console (which can be a laptop) is programmed to connect with the cloud platform so that images from the X-ray system can be uploaded to the cloud for processing and storage. The CAD software installed in the cloud server can “read” the CXR through the mechanism described in Section 1.2, usually extremely rapidly. The CAD output will then be transmitted to a laptop for review (Figure 5). In most cases, this laptop can also be the X-ray workstation. However, some X-ray system suppliers restrict any installation of third-party software, and thus require the use of a second device (laptop or tablet) for the CAD software. It is therefore crucial for implementers to involve the manufacturers of the existing digital X-ray system when selecting CAD software, to gain a correct understanding of the hardware requirement. The Stop TB Partnership is currently working with the manufacturers featured in the GDF catalog to refine options for integration.

A)



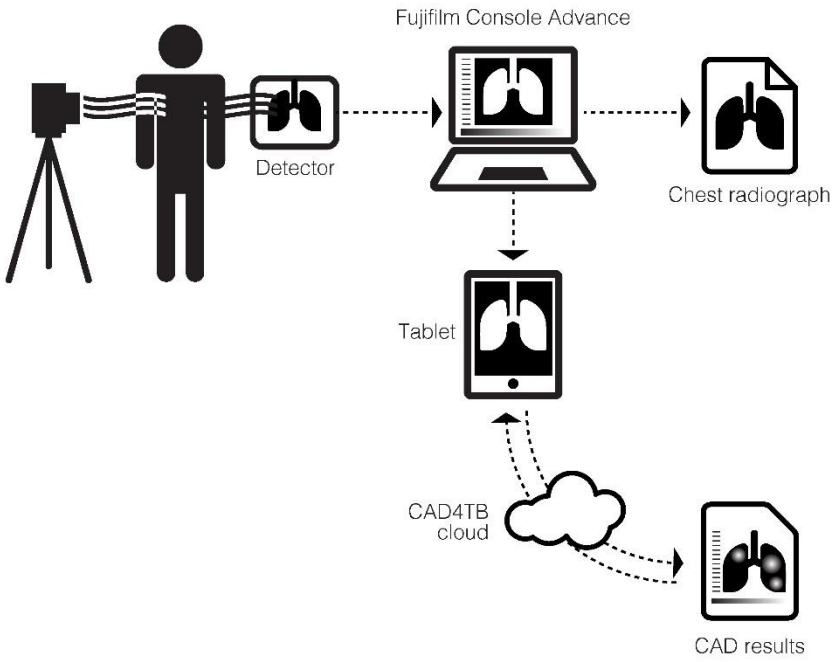


Figure 5. CAD operation in cloud mode. A) Viewing CAD results on the console computer. B) Viewing CAD results on a tablet computer.

Because X-ray files are rather large (roughly 10-30MB) a strong internet connection is needed for online (cloud) mode analysis by CAD. To compress the size of the DICOM before sending it to the cloud, DICOM lossless compression software, such as DCMTK (https://support.dcmtk.org/) – which is open-source and free – may be installed by the CAD suppliers on the X-ray console to significantly reduce internet traffic (bringing 15-20MB down to 4-5MB). However, some X-ray consoles do not allow for the installation of third-party software on their system; before installation, the X-ray system manufacturer should be consulted.

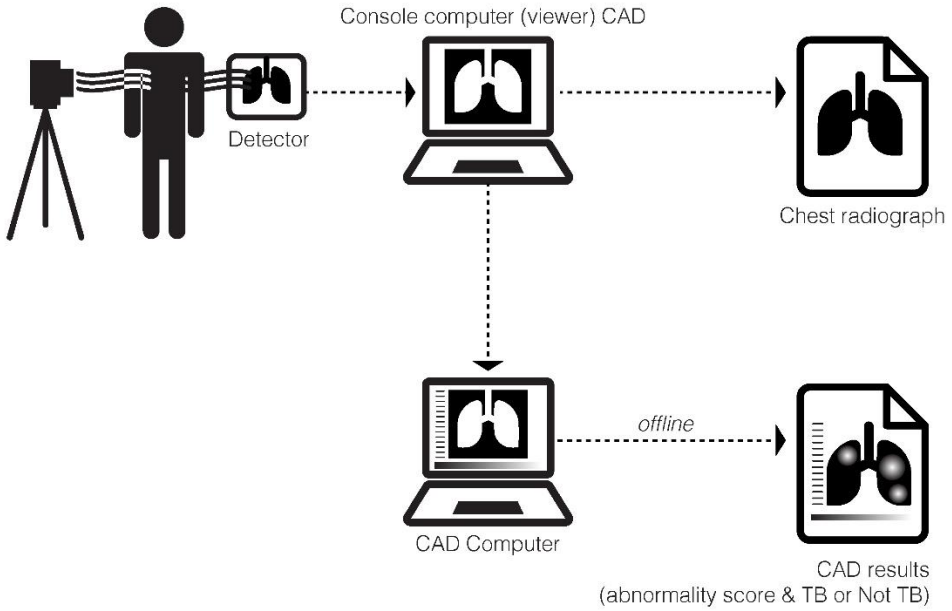
In settings with high-speed internet and a low-cost and unlimited data plan, the cloud mode is a good option which does not require high-performance equipment or large physical storage space, as required in the totally offline mode.

Offline mode

An offline mode is required in settings that either lack network access or have an unreliable internet connection, or where a data plan is limited or costly, or in areas where internet access is restricted, such as prisons. CAD4TB and InferRead DR Chest, the two systems available in the GDF catalog, can both be used offline. In offline deployment, CAD software installed locally on a dedicated processing box or laptop can receive CXR from the console laptop through a wired or wireless connection. The CAD laptop or box can “read” the CXR through the mechanism

described in Section 1.2. The CAD output will then be displayed directly on the CAD laptop or console laptop for review (Figure 6).

A)



B)

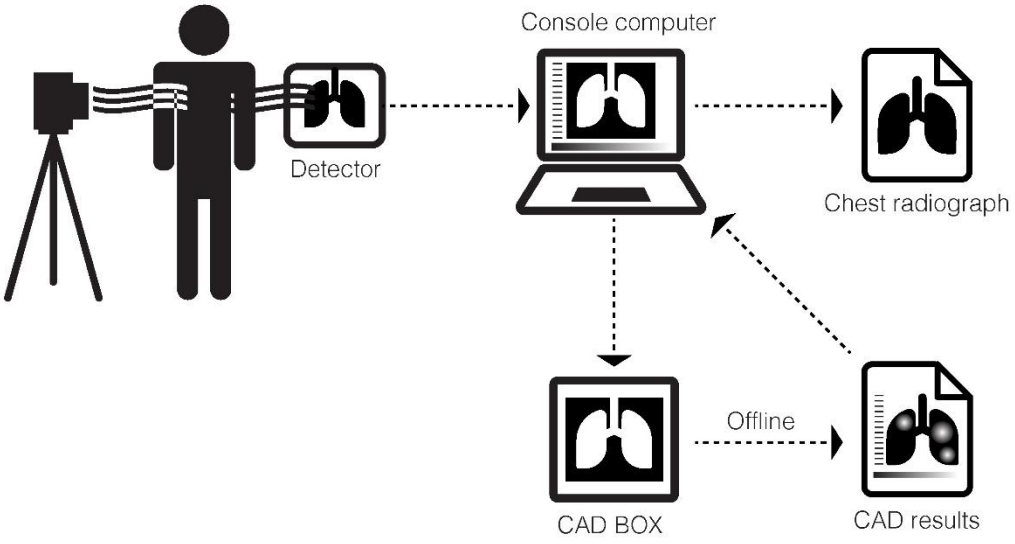


Figure 6 Offline CAD operation. A) Using a second computer with locally installed CAD software. B) Using an offline CAD box connected to the console computer.

In an offline set-up, at least two devices will be required.

Two-device offline mode: For offline modes, an additional hardware device (laptop, box, or processer) is required to run CAD software offline. This tends to be either because the X-ray system manufacturers do not allow third-party software to be installed on their hardware, or because, to run locally, the CAD software needs a more powerful processor with greater RAM, CPU, or GPU, and/or other considerations. This additional device has to be obtained separately when procuring the CAD software; it is provided by the supplier with the software pre-installed and a storage capacity of 30,000-60,000 CXR images. Depending on the device types, there are two set-ups:

1. **With a dedicated CAD box**: for CAD4TB, for example, it can also perform offline and is installed on a so-called CAD4TBbox (below), weighing roughly 1 kg, so that CXRs can be analyzed locally without an internet connection. Because the CAD4TBbox does not have a built-in battery, it needs an external power source.

   The CAD results can either be sent back to the console laptop, if there is a supporting viewer, or PACS or third-party software can be installed. Alternatively, the CAD output can be sent to a web-based viewer from the X-ray workstation. The standard configuration of the CAD4TB box includes a tablet for review of CAD4TB output. In rare cases, if the X-ray workstation is a closed system without access to external software, the tablet or any other device with a monitor should be connected to the CAD4TB box.

2. **With a dedicated CAD laptop:** InferVision, for example, provides a separate CAD laptop, weighing just under 2 kg, to analyze chest radiographs offline and is able to provide server/cloud data synchronization. The 15.6-inch HD laptop (238mm x 57.5mm x 19.8mm) is equipped with NVIDIA GeForce RTX 2070 Max-Q Refresh, 8 GB GD 1x Intel Core i7-10750H, 1TB internal hard drive (around 35,000-40,000 CXR). The laptop is further equipped with a 3-Cell Polymer Battery Pack, 73WH, which can run for up to 10 hours without external power, in an off-grid setting.

Hybrid mode

There is a slight variation in offline mode involving an option to synchronize and back up data on a pre-configured server on an occasional basis whenever an internet connection is available. Both CAD4TB and InferRead DR Chest can be operated in hybrid mode. When offline, both CAD4TB and InferRead DR Chest can be pre-configured to perform the CXR analysis locally (on an offline box or CAD computer) but automatically synchronize data for storage on a pre-defined server or central PACS system (see section 2.5) as soon as the internet is available. For example, upon user request, InferVision will set up and give access to a cloud backup server free of charge as part of the package. X-ray radiographs, InferRead DR Chest results, DICOM tag information in .csv file, and heatmap can be uploaded for storage on this server whenever there is Wi-Fi. This combines the ability to operate in regions with poor network connectivity with the benefit of backup on a cloud server (on an opportunistic basis, or, when appropriate, a regular, scheduled basis). For example, a project using ultra-portable X-ray systems with CAD for door-to-door screening

can use the CAD software offline to provide rapid results to the individuals being screened, while uploading to the server for storage at a later time.

Comparing the various installation options.

Table 6. Advantages and disadvantages of the different modes of CAD deployment

	Pros	Cons
Cloud deployment • In-country cloud server • CAD-supplier specific cloud server	• Easy to set up. • Less procurement of hardware, thus less hardware to maintain. • Can easily share with programme staff, remote radiologists, and other clinicians for a second opinion. • Version update is easier.	• Requires constant and stable internet connection because file size of individual CXR can be 10-30MB. • Fees include network or Wi-Fi cost. • Overall processing time (including upload and download) can be limited by internet speed. • Data privacy is more of an issue in cloud deployment as processes must be in place during set-up to de-identify images before transmission for cloud analysis and storage.
Offline deployment • Two-device offline mode • Fully integrated offline mode	• Can operate anywhere (no need for internet connection). • No need to purchase data plan or set up Wi-Fi.	• In most cases requires an additional piece of hardware. • Not easy to share with programme staff, remote radiologists, or clinicians for a second opinion. • Data backup and integration with surveillance system must be undertaken manually.
Hybrid: Offline reading + on-demand data synchronization	• Can operate anywhere without internet connection. • Can easily share with programme staff, remote radiologists, and other clinicians for a second opinion after synchronization.	• In most cases requires an additional piece of hardware.

Section 2.2 Pricing

This section includes the price of the CAD software in the GDF catalog that can be procured for a one-time payment (license-based pricing) with no further per-read cost. Fee-based pricing per read is an alternative offered by the supplier directly.

One InferRead DR Chest software perpetual license with unlimited readings for both online and offline use with the dedicated device for offline utilization (CAD laptop) (specifications in section 2.1 above) will cost USD 4,782, plus USD 248 for installation and training. Additional support and extended 3-year maintenance adds USD 522.

One CAD4TB perpetual license with unlimited readings for both online and offline use with the CAD4TB box will cost USD 15,500, plus USD 1150 for installation and training cost 1150 USD. Additional support and extended 3-year maintenance add USD 11,475. A discount is applied when a CAD4TB license is purchased with the Delft Light X-ray system (Chapter 3) – such that the CAD4TB box, worth USD 2,750, is provided free of charge and the support on the license is valid for 15 months instead of 12 months. When procuring the CAD4TB box, a 10-inch tablet is included as standard. If CAD4TB licenses are ordered in volume through the GDF catalog, a discount is applied (Table 7).

Table 7. Volume-based pricing discount for CAD4TB

Number of CAD4TB perpetual licenses purchased	**Price (per license) in USD**
1-9	$ 12,750.00
10-19	$ 11,475.00
20-49	$ 10,837.50
50+	$ 10,200.00

Section 2.3 Software Update

Unlike other types of screening and diagnostic tests, CAD software is constantly updated and improved, with new versions released fairly regularly, sometimes on an annual basis. When entering into agreements with suppliers, it is important to ensure that no extra costs will be incurred for new versions. For the two CAD software under discussion (CAD4TB and InferRead DR Chest), software patches, upgrades, and updates are included in the warranty, support & maintenance packages offered in the GDF catalog.

New versions will perform differently, and as discussed in Section 1.5, the selection of threshold scores may be different for new versions of the software. Fresh data and analyses are needed for each software update to provide the new range of scores and associated sensitivity and specificity values that will enable users to modify their threshold score to attain their previous target values when using the latest version. Stop TB's Digital Health Technology Hub aims to update evaluation results with every new CAD software update.

Section 2.4 Server and Storage

Given the medical nature of the information that is transferred, read, and stored, data privacy is a primary concern, particularly when data transfer involves cloud and hybrid deployment. As a result, countries are increasingly demanding that data storage and servers remain in the country of implementation, through a cloud or physical server, and most CAD suppliers do in fact offer the in-country server/cloud option. In any case, the various competing options should be weighed up judiciously. Implementers should be aware of the advantages of accepting use of the cloud provider recommended by a given CAD supplier, such as lower costs, ease of access for server updates, as well as better physical and logistical security measures.

In additional to the use of in-country servers, implementing partners should take other measures to reduce data privacy risks (please see Section 4.6).

Section 2.5 Integration with PACS System

CAD software can be integrated with existing PACS, RIS, and other legacy systems to automate the reading and reporting process. X-ray images are automatically routed to the CAD server for analysis (cloud or local device), then the CAD software receives and directs the result (score, heatmap, structural report, or other) back to PACS, RIS and other legacy systems.

Both CAD4TB and InferRead DR Chest are themselves simplified PACS systems. Should a separate professional PACS system be available, CAD suppliers can help set up the connection to the centralized PACS during installation.

Section 2.6 Compatibility with X-ray Systems and Validation

An optional validation may be performed involving both the CAD and X-ray system manufacturers to confirm the compatibility of the X-ray system with CAD prior to use. Image quality and CAD output accuracy may also be checked and confirmed during validation. If performance is deemed to be suboptimal by the CAD supplier, more data might be required to retrain the CAD software to fit the local conditions.

The integration of CAD software with ultra-portable X-ray systems offered in the GDF catalog is discussed in Section 3.5.

Chapter 3: Ultra-portable Digital X-ray Systems

Recent advances in X-ray technology have yielded increasingly portable devices that can be fairly easily transported to a peripheral field setting. The consequence is that, when these are used alongside CAD software, radiological assessments can now be conducted in remote areas cut off from vehicular access. This lifts much of the burden of travel that restricts some patients living in inaccessible communities from accessing TB services.

The new class of ultra-portable battery-powered X-ray systems can be carried in a small case, backpack, or even handheld. This cuts the high overhead costs formerly incurred when driving a large van or truck as required for previous X-ray systems. Perhaps more importantly, the **ultra-portable** design and **low weight** reduce physical strain on medical staff who need to carry and set up the equipment. When combined with a high-sensitivity digital radiography unit with advanced noise-reduction technology, this type of X-ray system can capture high-quality images despite the use of **low-dose radiation**. The reduced radiation exposure particularly benefits groups such as pregnant women, who were formerly excluded on account of the risks associated with exposure to the levels of radiation involved when undergoing CXR.

A recent landscape report by FIND outlines the features and role of these ultra-portable solutions in TB programmes.[21] In the chapter below, we focus on the two ultra-portable systems in the GDF catalog, **Delft Light** and **Fujifilm FDR Xair**, and provide a detailed discussion of the equipment and accessories offered when procuring the system as well as highlighting key aspects of implementation. This chapter concludes by clarifying how the CAD and ultra-portable systems available in the GDF catalog may be integrated to revolutionize TB programming, with a comparison of system combinations to aid decision-making.

Section 3.1 Equipment and Accessories

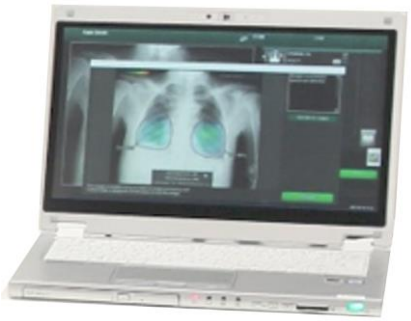
At its simplest, an ultra-portable X-ray system is a set of core components augmented by various accessories. The minimum core components are the X-ray generator, generator stand, X-ray detector, detector stand, a workstation (console) with imaging processing software, a carrying system (e.g., bags, case) and an external charging system (e.g., power bank, solar panel). Then the accessories will include supplementary batteries, protection products, and so forth.

FDR Xair by Fujifilm

Fujifilm FDR Xair is an ultra-portable X-ray system with ultra-lightweight **X-ray generator (FDR Xair XD2000), wireless FDR X-ray detector (FDR D-EVO II),** and **HP Console Advance (DR-ID 300CL)** with embedded **application software** (DX-CL, Virtual Grid and Dynamic Visualization II) for image processing. The software also has image editing features to optimize CXR images.

FDR Xair generator (XD2000)

FDR Xair detector: FDR D-EVO II



FDR Xair Console Advance DR-ID 300CL with application software DX-CL

All three components have built-in battery and can be operated off-grid for a limited period of time. Both the detector and generator feature a 'sleep' mode which begins automatically after 10 minutes of inactivity. Although the labelled maximum number of exposures is 100, early implementers have noted a much smaller number of exposures (30-40) when only operating on battery. Additional power sources should be brought to field settings without mains electricity, and according to the manufacturer these can provide an additional 300 exposures (see below).

Fujifilm advises operating the generator on specific power settings, with three pre-set settings provided, depending on the area of the body targeted. The first pre-defined setting is the default

(0.5mAs/90kV), suitable for chest X-ray. However, exposure settings can be changed depending on patient body size. There are two other pre-defined settings which are for abdomen and limbs respectively.

After exposure, users can check the images on the console monitor immediately, though the generator requires a cycle time of around 10 seconds between patients.

Supporting Stands: Although both the generator and detector could be operated without a supporting frame or stand, it is highly recommended that both be used on a supporting stand. Use of the generator stand together with the included stretchable exposure release switch allows for remote operation of the generator, at a distance of 2.5m. A supporting frame for the detector is a good addition to maintain a safe distance and angle between the patient and the generator. It also prevents physical damage from a fall or dropping, especially when taking images of sick patients, or children who may not even be able to hold the panel.

The stands available via the GDF catalog are lightweight and collapsible, designed for ease of transport in the field.

Carbon stand for FDR Xair generator

Carbon stand for FDRX-Ray detector

Exchangeable detector battery and charger: For radiation safety reasons, the battery inside the Xair generator is fully integrated and can only be replaced by trained Fujifilm service engineers. Meanwhile, a replacement battery for the detector is provided with the system and can be used to extend detector use in the field, simply by inserting it in the back panel. Implementers can use the battery charger to fully charge one battery in approximately four hours.

Battery for FDR Xair detector

Battery charger for FDR Xair detector

Power bank for FDR Xair

FDR Xair power bank: An RAV-Power power bank (20,000mAh) is provided with the system in the GDF catalog that can recharge all electrical components in the system. The current version of the system allows for X-ray exposure and charging to occur simultaneously, unlike older models. According to the manufacturer, the generator can take an additional 300 exposures with the addition of the power bank.

Carrying case: The carrying case provided with the system allows easy transport of the X-ray system and accessories and can be carried on a mini carry cart.

FDR Xair core system in its case

<u>Radiation Safety Equipment:</u>

One protective lead apron and ten shock detection stickers are provided when procuring the complete Fujifilm FDR Xair system from GDF. At least one water-resistant, durable and portable Radiation Warning Sign, mentioning radiation hazard and pregnancy, will be included with any X-ray system provided through GDF.

Protective lead apron (front view)

Protective lead apron (side view)

Shock sticker

Detailed product specifications are given in Annex 3. The manufacturer's user manual can be found here.

Delft Light by Delft Imaging

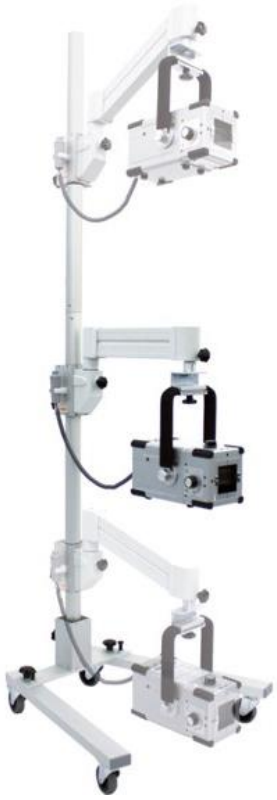
The Delft Light is an ultra-portable X-ray system that can be deployed in various settings. It comprises X-ray generator TR 90/20 (manufactured by Mikasa), X-ray detector CXDI 702-C with accompanying application software (Canon NE) and HP laptop.

Delft Light generator:	Delft Light detector:	Delft Light workstation:
TR90/20	Canon CXDI 702c	Canon NE

Each component has its own built-in battery, allowing off-grid use for a limited period of time. The generator battery has greater capacity than that of the Fujifilm FDR Xair and will offer more than 200 exposures. Although the detector battery is smaller, offering roughly 100 exposures, twice that number will be possible in the field, because two batteries are supplied as standard. The duty cycle of the Delft Light is 1:60, meaning one exposure lasting approximately one fifth of a second is possible every 12 seconds.

Supporting stands: The Delft Light system procured through GDF includes an aluminium mobile stand for the generator, and a portable hanger for the detector panel (see below).

The mobile stand for the generator is fully counterbalanced with a spring arm for height adjustment, is capable of 360-degree rotation, and can be dismantled for transport in its own bag (supplied). Use of a generator stand together with the included detachable hand switch allows for remote operation of the generator at a distance of 3m. For portability, the VersariX portable detector panel hanger is provided, rather than a detector stand. The strap and sturdy hook can be used to suspend the detector from improvised mounts, such as walls or doors, and can be adjusted vertically (40cm-200cm range).



Mobile stand for Delft Light generator

Portable panel hanger (VersariX) for Delft Light detector

Mobile stand for Delft Light generator in its bag

Exchangeable battery and battery charger: Two replacement batteries for the detector are provided with the system. The battery charger can charge two batteries simultaneously to increase workload in the field if needed. The X-ray generator tube battery must be removed from the tube for charging and inserted into the generator charger.

Battery chargers for Delft Light generator and detector

Solar panel: In remote TB screening settings, all system components (X-ray generator, detector, workstation and CAD4TB box) can be recharged from a portable Mobisun solar panel (with built-in power bank). Unfortunately, solar charging cannot occur during operation. The unit, which is water resistant, takes 16 hours to fully charge in direct sunlight. Alternatively, it can be charged from the grid in roughly 2.5 hours.

MobiSun solar panel and power bank

Key features:	
Output	230 VAC @ 250 Watt. 2 USB ports (5 Volt, 3.2 Amp)
Peak Power	500 Watt
Battery capacity	70 Ah, 256 Wh
Dimensions	550 x 300 x 50 mm
Weight	6 kg

Carrying case/bag: all Delft Light components (X-ray generator, detector, detector stand, console, and accessories, including CAD4TB box) can be packed into a single backpack, except the generator stand, which has its own bag for transport (see above).

Backpack

Interior of backpack

Radiation Safety Equipment: One protective lead apron, five portable radiation hazard warning signs, and ten shock detection stickers are provided with the Delft Light system.

Detailed product specifications are given in Annex 3. The system user manual can be found here.

Section 3.2 Implementation Considerations

Portability

Ultra-portable X-ray systems are often justifiably marketed for their portability, but it would be misleading to stress their ability to be packed into a single carrying case or backpack. This is because a complete set can still be too heavy for a single person to carry comfortably: or carry at all, especially when heavy supporting frames are needed. The basic Fujifilm FDR Xair set-up (a generator, a detector, a console laptop, and a lead apron, along with the lightest stands) weighs in at **29.4** kg, while the Delft Light option weighs **33.2** kg in total. Table 8 outlines the weights of individual devices and components.

Table 8. Weight of system components (kg)

	Fuji FDR Xair (kg)	**Delft Light (kg)**
X-Ray Generator	3.5	7.0
X-Ray Generator Stand	1.7	8.0
X-Ray Detector (incl. batteries)	3.4	3.8
X-Ray Detector Stand	3.0	0.4
Console laptop / workstation	1.25	1.5
Lead apron	4.9	3.0
Battery charger(s)	0.5	1.0
Solar panel / power bank	0.67	6.0
Carrying case (empty)	10	2.5
Others (e.g. AC adaptor)	0.51	
Total	**29.4**	**33.2**

Electrical Power

In the absence of an electricity grid and external power bank or solar panel, the number of X-ray images that one system can collect in the field will depend on the battery capacity of the system's various components as well as their operating power. The X-ray generator, detector, console laptop and CAD device all have built-in batteries, the capacity of which varies depending on the system (Tables 9A & 9B below). There are some supplementary power sources that are provided in the Full Kit can be used to provide additional power; for example, a fresh set of detector batteries can be inserted to double the operating time of the X-ray detector. Notably, the Delft Light generator battery must be taken out periodically for recharge, and although FDR Xair can be charged while in operation, its capacity is limited in the absence of a mains power supply (Table 9A). Clearly, reliance on battery power is currently the factor most likely to limit throughput in the field. Consequently, in off-grid field settings where additional power sources cannot be carried, ultra-portable X-ray systems are generally best suited for **lower screening throughput** (settings that require no more than 50-200 X-ray scans per day).

Furthermore, in terms of CAD, the CAD4TB box requires **AC power connection**. However, according to the manufacturer, InferRead DR Chest, which is installed on a separate laptop with built-in power, allows 10 hours without charging according to the supplier.

Table 9A. Exposures possible in the field on a single battery or set of batteries, and recharging time needed.

Ultra-portable X-ray systems

	Fujifilm FDR Xair	Delft Light
Generator	Approx. 100 exposures * Additional 300 exposures claimed possible by using a fully-charged power bank to recharge. Recharge: approx. 4.5h	Approx. 200 exposures Recharge: approx. 4 hours (cannot be recharged while in operation).
Detector	Approx.100 exposures per standard set of two batteries. 100 further exposures possible using the replacement detector batteries. Recharge: approx. 3h	Approx.100 exposures per standard set of two batteries. 100 further exposures possible using the replacement detector batteries provided with the full kit package. Recharge: approx. 2.5h

** However, early implementers found that battery capacity allowed them to take only 30-40 exposures.*

In addition to the charging requirements of core system components like the generator and detector (Table 9A), the battery capacity of other necessary hardware, including that required for offline CAD operation (Table 9B), could limit operations in field settings without power.

Table 9B. Maximum capacity of the in-built battery of the offline CAD hardware

InferRead DR Chest Laptop	CAD4TB Box
10 hours continuous use	AC power connection required

Radiation Safety

Radiography involves exposure to ionizing radiation, which may increase the long-term risk of cancer, though the risk remains extremely low when the levels of radiation are controlled. Therefore, radiation risks to patients, workers and the public from the medical use of X-rays must be mitigated by conformity to radiation safety standards. CXR delivers a radiation dose to the patient well below 0.1 mSv, which corresponds to 1/30th of the average annual radiation dose from the environment (3 mSv) and 1/10th of the annual dose limit for the general public (1 mSv).[4] The global benchmark for radiation safety worldwide is Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards (BSS) published by the International Atomic Energy Agency (IAEA) in 2014. In 2018, IAEA published Radiation Protection and Safety in Medical Uses of Ionizing Radiation – Specific Safety Guide SSG-46 to provide practical guidance to support the implementation of the BSS in medical applications of radiation.

Both Fujifilm FDR Xair and Delft Light have a reduced level of output power and emit less radiation than stationary hospital machines. The stretchable hand switch on the X-ray generator also allows for remote operation at a distance of 2.5m to 3m, further reducing radiation risk for the operators. Information about the radiation exposure of both products can be found here.

Local radiation safety rules and regulations must be consulted and complied with and evidence-based imaging guidelines should be considered. Furthermore, as a matter of protection policy, no more radiation should be used than necessary to obtain images of adequate quality.

Despite the reduced power output, a more sensitive detector allows image quality comparable to that of conventional stationary systems, according to early implementers (see Chapter 6).

Workstations also include software tools that can be used to optimize the image. Example CXRs taken with the FDR Xair and Delft Light are provided here.

Console

The console laptop of both systems is set up exclusively for the receipt of CXR images from the system. No additional software should be installed, nor should it be connected to additional hardware without first consulting the X-ray supplier. Unauthorized and unsupervised installation of third-party software can cause system failure, necessitating return to the manufacturer for repair.

Section 3.3 Pricing

The Fujifilm FDR Xair system – full kit (with accessories) in the GDF catalog – costs approximately USD 47,000, with a one-year initial warranty, comprising:

- FDR Xair generator (XD2000 portable E)
- FDR Xair generator carbon stand
- FDR Xair detector (D-EVO II DR-ID 1211 SE A-E)
- FDR Xair detector carbon stand
- FDR Xair Console Advance (DR-ID 300CL) with application software DX-CL
- FDR Xair system carrying case
- FDR Xair power bank
- Protective lead apron
- Portable radiation warning sign
- Shock stickers

Any FDR Xair system should be procured together with an Installation and Training package costing roughly USD 2,000.

The Delft Light – full kit (with accessories) in the GDF catalog costs approximately USD 66,750 with a one-year initial warranty, comprising:

- Delft Light generator (TR90/20)
- Delft Light generator mobile stand
- Delft Light detector (Canon CXDI 702-c)
- Delft Light detector VersariX portable panel hanger
- Delft Light workstation Canon NE
- Delft Light software Canon NE
- Delft Light backpack
- Mobisun solar panel
- Protective lead apron
- Portable radiation warning signs
- Shock stickers

Any Delft Light full kit should be procured together with an Installation and (remote) Training package costing USD 2,500.

Finally, if Delft Light full kits are procured in volume through the GDF catalog a discount is applied (Table 10). This is not available for the Fujifilm FDR Xair.

Table 10. Volume-based pricing discount for Delft Light

Number of Delft Light full kits procured	Price (per item) in USD
1-4	$ 66,750.00
5-10	$ 66,057.50
11-19	$ 65,365.00
20-49	$ 64,672.50
50+	$ 63,980.00

The warranty agreement covers all components and accessories (except in the event of misuse). This includes corrective maintenance, spare parts, shipment to site, disposal of faulty parts, cost of replacement work, personnel transport and arrangements, software patches, upgrades and updates (excluding CAD software). To extend the warranty beyond the initial

12 months, 1-year or 3-year warranty extensions can be procured through GDF. For Delft Light, these warranty extensions have to be procured while the initial warranty period is still valid, while for Fujifilm FDR Xair, these warranty extensions must be purchased at the time of procuring the FDR Xair system itself. The extended warranty includes one remote session per year of preventative maintenance.

A one-year extension costs roughly USD 5,000 for either system, whereas a three-year extension for the Fujifilm FDR Xair costs USD 15,000, compared to USD 27,834 for Delft Light.

Section 3.4 Compatibility of CAD Software and Ultra-portable X-ray Systems

The GDF catalog includes two CAD software packages and two ultra-portable X-ray systems and therefore allows for four possible combinations that integrate CAD software and an ultra-portable X-ray system. The configuration and hardware required to integrate products depend on the combination of ultra-portable X-ray system and CAD technology and whether the integrated system will be used in an online or offline set-up.

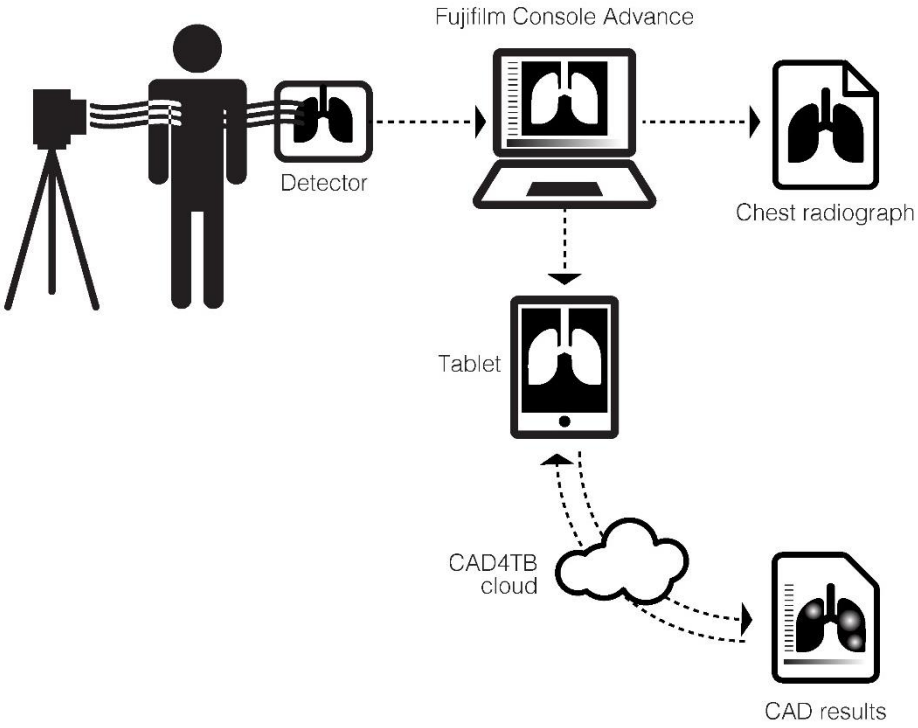
Online

When using the two products online, the configuration with Delft Light simply requires that one laptop (the Delft workstation) be linked to the appropriate cloud server (either InferRead DR Chest or CAD4TB). The Delft X-ray workstation will receive X-ray images and immediately transmit these to the server for analysis by CAD software. The CAD output will then be displayed on the same device, as depicted in Figure 5 (Section 2.1).

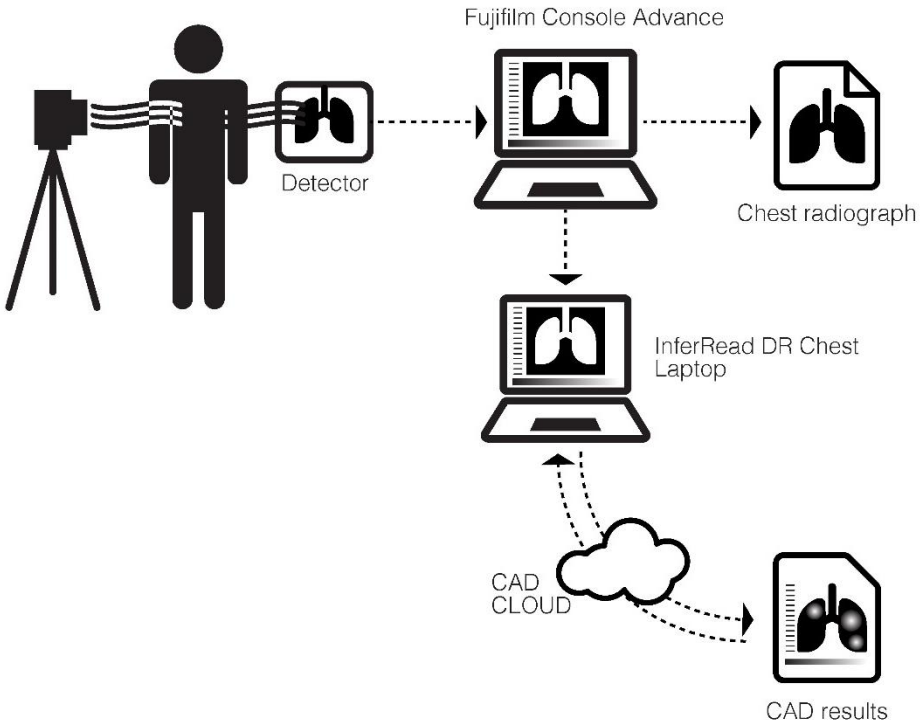
However, for Fujifilm FDR Xair, another device (laptop or tablet) is needed in addition to the Fujifilm Console Advance in order to access the CAD cloud server (either InferRead DR Chest or CAD4TB). The second device will receive the X-ray images from the Fujifilm Console Advance and CAD output from the cloud.

Figure 7. Online mode hardware needs and configuration for Fujifilm FDR Xair with CAD4TB and InferRead DR Chest.

Fujifilm FDR Xair integrated with CAD4TB – online Mode



Fujifilm FDR Xair integrated with InferRead – online mode

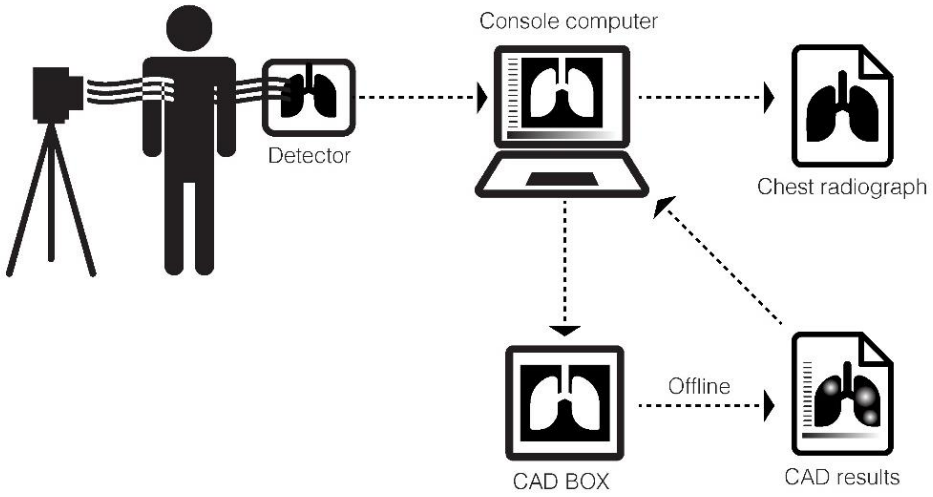
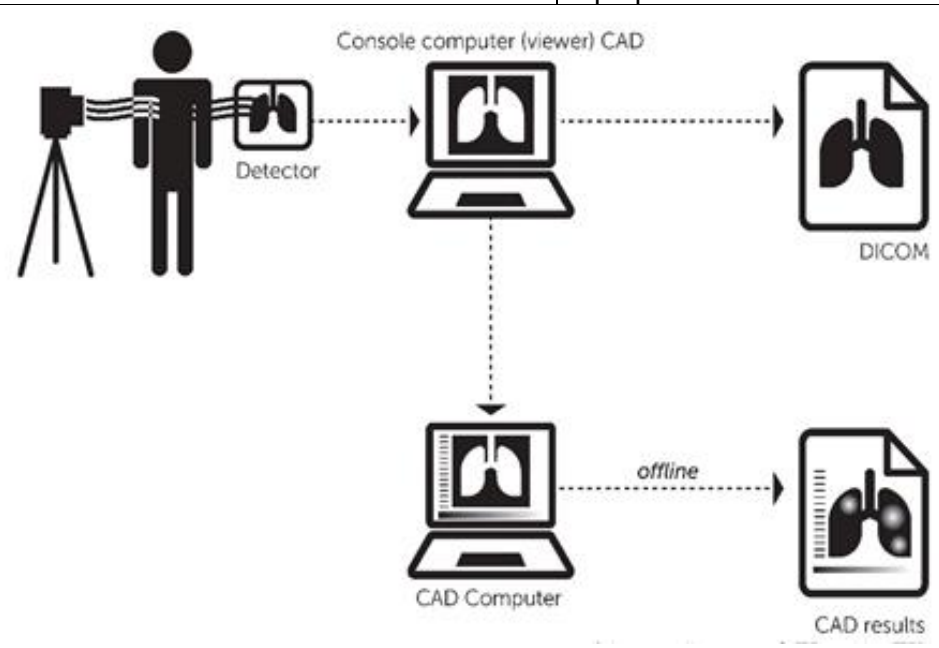


Offline

Offline integration configurations are more complicated because an additional device is always required. When using CAD4TB, only a CAD4TB box (weighing 1 kg) is required for CAD operations, in addition to the Delft Light or Fujifilm FDR Xair systems. However, when using InferRead DR Chest, the CAD laptop (weighing 2 kg) is needed (Table 11).

Table 11. Four offline integration configurations and their approximate weight.

	Ultra-portable X-ray system	
	Delft Light	**Fujifilm FDR Xair**
CAD4TB by Delft	**Weight:** 33.2 kg + 1 kg	**Weight:** 29.4 kg + 1 kg
	Offline set-up: Delft Light workstation + CAD4TB Box. CAD results and CXR display on Delft Light workstation	**Offline set-up: FDR Xair** Console Advance + CAD4TB Box. CAD results and CXR display on the **FDR Xair** Console Advance

<table>
<tr><td></td><td colspan="2"> 
</td></tr>
<tr><td rowspan="3">InferRead DR Chest by Infervision</td><td>Weight: 33.2 kg + 2 kg</td><td>Weight: 29.4 kg + 2 kg</td></tr>
<tr><td>Offline set-up: Delft Light workstation + CAD laptop.
CAD results and CXR displayed on the two separate laptops.</td><td>Offline set-up: FDR Xair Console Advance + CAD laptop.
CAD results and CXR displayed on the two separate laptops.</td></tr>
<tr><td colspan="2"> 
</td></tr>
</table>

A simplified diagram of the configurations is summarized in Annex 4.

Section 3.5 Comparison

When deciding which set-up to buy, the features of both the CAD and ultra-portable X-ray system should first be assessed in isolation. For the X-ray system, that means, for example, portability and battery life; while for CAD software that would involve, for example, the published software accuracy. Then the benefits and drawbacks of an entire combination must be weighed (cost, ease of integration, hardware requirement). The pros and cons of each integrated set-up are shown in Table 12 (with estimated prices for the full package, inclusive of installation, training, and three-year extended warranty).

Table 12. The advantages, disadvantages, and total price of each of the four combinations of CAD software and ultra-portable X-ray systems available from the GDF catalog.

		Ultra-portable X-ray system	
		Delft Light	**Fujifilm FDR Xair**
CAD Software	**CAD4TB by Delft Imaging**	**Total cost: ~$123K**	**Total cost: ~$93k**
		Pros: • X-ray generator has a battery with greater capacity, allowing a higher number of exposures (200) than FDR Xair (100), ideal for large throughput setting. • X-ray generator has greater voltage range (40-90kV). • Requires one laptop (Delft Light workstation) for online use and an additional device, CAD4TB box, for offline use. • The CAD4TB box is free of charge when CAD4TB software license is procured with Delft Light X-ray. • Published research data suggests that CAD4TB is more accurate in classifying if TB-suggestive abnormalities present on a CXR than InferRead DR Chest (Section 1.5).	**Pros:** • Most portable option (approx. 29 kg) and second least expensive. • Fujifilm FDR Xair is lighter than Delft Light. • Has lightweight power bank (0.67 kg) to power the system for offline use. • Proper detector stand (rather than hanger). • Published research data suggests that CAD4TB is more accurate in classifying if TB-suggestive abnormalities present on a CXR than InferRead DR Chest (Section 1.5).
		Cons: • The most expensive option. • Delft Light is heavier than Fujifilm FDR Xair. • The detector support is only a panel hanger, not a stand.	**Cons:** • Limited generator battery capacity, not suitable for large throughput and off-grid setting without a power bank. • X-ray generator has lower voltage range (50-90kV).

		• When used offline, the CAD4TB box requires an AC power supply, which implies carrying the solar panel to the field (total weight approx. 34 kg). • Only classifies if TB-suggestive abnormalities present on a CXR (a separate score is not provided for non-TB abnormalities).	• Requires two devices for online use (a console laptop and a tablet / laptop). • Only classifies if TB-suggestive abnormalities present on a CXR (a separate score is not provided for non-TB abnormalities).
	InferRead DR Chest by Infervision	**Total cost: ~$103K** **Pros:** • X-ray generator has a battery with greater capacity, allowing a higher number of exposures (200) than FDR Xair (100), ideal for large throughput setting. • X-ray generator has greater voltage range (40-90kV). • Requires only one laptop (Delft Light workstation) for online use. • Non-TB abnormalities (e.g. nodule) are also reported although the accuracy is not validated by independent evaluation. • Although the CAD laptop is heavier than the CAD4TB box, the in-built laptop battery can run up to 10 hours in an off-grid setting, making it possible not to carry the solar panel to the field (that reduces total weight brought to the field to roughly 27 kg). • Less expensive than above option.	**Total cost: ~$70K** **Pros:** • Fujifilm FDR Xair is much lighter and portable than Delft Light. • The cheapest option and just 1 kg heavier than the FDR Xair and CAD4TB option. • Proper detector stand (rather than hanger). • Non-TB abnormalities (e.g. nodule) are also reported although the accuracy is not validated by independent evaluation.
		Cons: • Delft Light is heavier than Fujifilm FDR Xair. • The detector support is only a panel hanger, not a stand. • Requires a dedicated CAD laptop for offline use (rather than CAD4TB box, compared to the above). • Published research data suggests that InferRead DR Chest detects TB-associated abnormality less accurately than CAD4TB (Section 1.5).	**Cons:** • Limited battery capacity, not suitable for large throughput and off-grid setting without a power bank • Lower generator voltage range (50-90kV) • For both online and offline use, requires the CAD laptop in addition to the FDR Xair Console Advance.

		• Though InferRead DR Chest has been used in the field, there is less published field experience with this combination.	• Published research data suggests that InferRead DR Chest detects TB-associated abnormality less accurately than CAD4TB (Section 1.5)

Chapter 4. Planning and Preparation

In this chapter, we offer a menu of the key programmatic, procedural, and monitoring and evaluation (M&E) steps to consider when designing and implementing a project to deploy ultra-portable X-ray systems with CAD software.

Section 4.1 General Operational Considerations

When planning an intervention involving CAD and ultra-portable X-ray systems, several vital preparatory considerations need to be thought through: and acted upon. These are listed below, though not in strictly chronological order, because several steps can usefully be undertaken simultaneously. External technical assistance may be needed. Annex 5 is a summary list of relevant budgetary implications.

Situation assessment should be conducted to assess existing public health interventions, available literature and policy on CAD and X-ray screening, existing health system integration and capacity, and existing ICT infrastructure. Details are discussed in Section 4.2.

Procurement and Importation

1. Perform a market analysis of available ultra-portable X-ray systems and CAD software to identify: the number and types of suppliers available; pricing structures; total costs of ownership.
2. Procure and select ultra-portable X-ray systems, CAD software, service, and maintenance plans. Annex 2 provides an example tender template for CAD software.
3. Place orders for ancillary items to be procured locally, including data backup devices or systems, barcode machines, printers, and recruitment as needed.
4. Integrate the X-ray system with CAD software with the help of the suppliers.

Registration and Validation

5. Ensure any regulatory requirements have been met to allow for importation (may require approval from national Radiation or Nuclear Authority), as well as compliance with any policy governing the use of CAD software for TB screening and triage.
6. Approval of use from the Radiation / Atomic Energy Regulatory Authority or equivalent might be required in addition to market authorization. Such authorization might be different for indoor use and outdoor use.
7. Design radiation safety protection measures with Radiation / Atomic Energy Regulatory Authority or equivalent for patient, and operator. Such measures might need to be different for indoor use and outdoor use.
8. Design a methodology for in-country demonstration of CAD software reading, if needed, and selection of operating points.

Human Resources (HR)

9. Identify and hire X-ray technicians or radiographers to operate X-ray systems, and community healthcare workers to conduct screening activities. If used for screening and triage purposes, radiologists might not be required to be on-site according to WHO recommendation.
10. Identify existing biomedical and IT staff (or hire new staff) to support the configuration, installation, maintenance and support of ultra-portable X-ray systems and CAD software.

11. Ensure sufficient staff (bare minimum: a two-person team) to transport ultra-portable X-ray systems and necessary accessories.

Training

12. Source or develop training materials on implementation, selection of operating points, and interpretation of CAD outputs for clinicians and community healthcare workers engaged in TB screening and triage. The X-ray system and CAD manufacturer should also provide training.
13. Train radiographers and community healthcare workers on the proper use and transport of ultra-portable X-ray systems, as well as radiation safety and protection.
14. Prepare training for biomedical and IT staff on system maintenance, digital X-ray system and CAD output storage.
15. Organize training of community cadres and healthcare workers at facilities receiving patients referred by X-ray & CAD technology screening.

Site preparation

16. Use a standardized checklist to assess site suitability (see template, Annex 6).
17. Finalize patient referral pathway, and all links accordingly, as well as equipment needs for confirmatory TB testing, and image printing if requested at referral facility.
18. Ensure data storage and backup at referral facility.
19. Use a standardized checklist to assess site readiness (see template, Annex 7).

Data reporting and security

20. Revise any algorithm, guidelines, registers, or forms governing the use of X-ray CAD technology for active case finding, as well as the policy for reading and interpretation of CAD output.
21. Agree on screening algorithms including the intended use case and setting for the CXR-CAD technology
22. Develop project-specific Confidentiality Agreement, and Data Processing Agreement (DPA) or Data Usage Agreement (DUA) compliant with local data laws and regulation and/or Health Insurance Portability and Accountability Act (HIPAA) and/or General Data Protection Regulation (GDPR). The Stop TB Partnership have developed template Confidentiality Agreements and Data Processing Agreements (Section 4.6).
23. Understand how data will be stored: locally, or on CAD servers provided by the suppliers, or linked to the country's existing PACS system.
24. Make modifications on site to any electronic registers (presumptive TB registers, ACF register, community referral forms)

M&E

25. Prepare a monitoring and evaluation (M&E) plan and a quality assurance system. Annex 8 proposes an M&E framework.
26. Ensure reporting of X-ray systems workload and CAD reading results.

27. Plan for regular monitoring of active case finding (ACF) Project/NTP, and supervisory visits.
28. Provide supervisory technical and radiology support to monitor use, identify challenges, and maintain the highest quality of image and CAD scoring.

Section 4.2 Situation Assessment

When considering the introduction of a digital health solution such as CAD, there is more at stake than the software itself. It has to slot into available information and communication technology (ICT) infrastructure and fit into the broader context of a given health system. As an initial step, a country situation analysis should be conducted to select possible sites for implementation. This analysis should cover the following:

1. **Existing public health interventions**
   - TB programme activities, especially screening and diagnosis at the administrative level in public and private sectors.
2. **The available literature on CAD and X-ray screening**
   - Peer-reviewed journal articles comparing the most recent versions of CAD products.
   - International guidelines and reports on the use of CAD software for TB screening, particularly the latest WHO guidelines.
3. **National and district regulations and policy**
   - Policies relevant to X-ray systems and CAD technology, including those related to X-ray system operation and safety, and general policies surrounding data privacy (including the transfer of data internationally).
   - The existence of targets for expanding access to diagnosis and care, including the use of X-ray technology for TB screening.
4. **Existing health system integration and capacity**
   - Country practices and algorithms involving X-ray systems and CAD software for TB screening and triage, such as reporting procedures.
   - Available and accessible capacity in private systems, occupational health systems, and so forth.
   - Physical infrastructure: availability and distribution of X-ray systems.
   - Radiographers to operate those X-ray systems.
   - Mobile screening units (if any).
   - Radiologists to interpret chest X-rays, noting where CAD software could fill a gap.
   - Laboratories for specimen referral and confirmatory diagnostic testing such as Xpert MTB/RIF or Truenat.
5. **Existing ICT infrastructure**
   - Institutional ICT infrastructure including Picture Archiving and Communication System (PACS), Radiology Information System (RIS), or other existing radiology systems.
   - ICT infrastructure, including internet accessibility, at the various administrative levels.

Reviewing the existing situation should make it possible to:

6. **Select possible implementation sites**
7. **Establish relationships with nearby facilities for:**
   - storing backup X-ray images and CAD software reading outcomes
   - referral of people for confirmatory testing (such as community to facility; primary healthcare to facility; or diagnostic site to Basic Management Unit).
8. **Establish the roles and responsibilities of the NTP, local distributors and implementation partners** (see section 4.3 for a suggested stakeholder framework).
9. **Develop a costed operational plan for implementation, including funding required for Implementing Partner activities.**

The use at lower levels within a health system of CAD software and ultra-portable X-ray systems, alongside other emerging portable confirmatory diagnostic tools (such as the battery powered Truenat TB assay) will decentralize screening and detection of TB, and with appropriate planning and funding, will vastly increase public access to sensitive screening and diagnostic tools.

Section 4.3 Stakeholder Framework

A stakeholder framework should outline all relevant organizations, describing the role of each, so as to ensure selection of the right partners, and integrate the newly implemented technology into current work streams and processes from the outset. Below is an example of a stakeholder framework for the implementation of ultra-portable X-ray systems with CAD software.

Table 13. Stakeholder Framework

Area	Stakeholder	Role	Role in implementation of CAD in TB
Governmental bodies	National TB Programmes (NTP)	Supporting	• Coordinate the various aspects of implementation of ultra-portable X-ray with CAD technology with the overall aim of increasing case detection. • Develop CXR-CAD technology implementation algorithm, update with relevant information, secure approval of national protocols by the Ministry of Health. • Train medical staff in using ultra-portable X-ray with CAD. • Validate CAD X-ray results and ensure appropriate case management for people diagnosed with TB. • Monitor, evaluate and adjust the intervention as per country needs and lessons learned.
	Ministry of Health	Supporting	Oversee the implementation of the NTP and issue relevant documents to enable ultra-portable X-ray with CAD as part of the NTP strategy.
	Medicines and Medical Devices Agency or equivalent	May not be required depending on the country	• Confirm whether CAD software is classified as a medical device in the country. If necessary, complete national registration. • Confirm if ultra-portable X-ray systems require local registration and market authorization. If so, effect registration and approval.
	National Radiation/ Atomic Energy Regulatory Authority or equivalent	Supporting	• Confirm if the ultra-portable X-ray systems can be imported (from a radiological safety standpoint). • Design radiation safety protection measures for patient and operator.
	National Centre for Personal Data	May not be required depending on the country	Confirm whether ultra-portable X-ray with CAD technologies must be registered as medical devices that use personal data. If required, effect registration.

Area	Stakeholder	Role	Role in implementation of CAD in TB
	Protection or equivalent		
	University, teaching hospital	May not be required depending on the country	Update training curricula with the relevant information on ultra-portable X-ray with CAD and train clinical staff accordingly.
Professional associations	National TB Association / Society	Supporting	Promote ultra-portable X-ray with CAD among TB specialists; conduct research on how it impacts case notification.
	National Radiography and Radiology Associations or equivalent. National Medical Association or equivalent.	**May be opposing**	Medical professional associations should be engaged and sensitized to ensure support for ultra-portable X-ray-CAD projects. Engagement should include radiographers, radiologists, chest specialists and relevant clinical officers specialized in lung health.
ICT companies	Internet companies	Neutral	Provide internet connection for running CAD software and data synchronization
In-country implementers	Principal local implementing partners and other implementing partners	Supporting	• Form a working group to define specifications of ultra-portable X-ray with CAD technology needed in view of national health outcome goals, country context and local settings. • Procurement and supply management. • Organize training for medical staff on using ultra-portable X-ray system with CAD software in TB. • Overall implementation.
	Civil society and TB-affected community organizations	Supporting	ACF activities and advocacy for sustainable funding of the intervention to ensure timely TB detection.
Insurance	National Health Insurance Fund	May not be required depending on the country	Cover expenses related to CAD in TB (investigations, maintenance) for sustainability.
Funders and Investors	The Global Fund to Fight AIDS, Tuberculosis and Malaria/ USAID / Stop TB Partnership	Supporting	Provide funding for CAD software procurement and investigations, if required.

Area	Stakeholder	Role	Role in implementation of CAD in TB
Other international partners	WHO, Stop TB Partnership and others	Supporting	Issue relevant guidelines related to use of CAD technology in TB. Providing technical assistance on various aspects in the implementation.

Section 4.4 Registration

A country should work closely with the manufacturer and authorized distributors to clarify importation and registration requirements, and to initiate any country verification required. Regulatory procedures in most countries are more standardized for the registration and importation of an X-ray system than they are for CAD software. However, as X-ray systems emit radiation, approval may be required from the local nuclear authority in addition to market authorization. Some countries are able to waive the registration requirement when procurement is through a reputable agency, such as the United Nations. Others will need to conduct verification studies, albeit usually on a small scale.

Section 4.5 Site Preparation and Assessment of Readiness

As part of the situational analysis, an example checklist is provided in Annex 7 to help implementers to assess site suitability. Following completion of all implementation steps (Section 4.1) and prior to beginning X-ray screening, the site and staff should be evaluated for readiness.

One of the most important infrastructure considerations for site selection is **electrical power.** This is less a concern if the system is deployed in a setting with access to mains electricity. However, as described in Section 3.2, if implementers plan to deploy the systems for high throughput in an off-grid setting, external power sources are critical to ensure continued operation.

When using CAD products online or in hybrid mode, **internet availability** is an impact implementation factor to consider. A strong and stable internet connection is required for online mode because X-ray files are rather large (roughly 10-30MB). If the intended use is in remote areas without reliable internet access, it is important to purchase a CAD product that can analyze CXR images and generate results locally offline.

Another important factor to consider is **radiation safety.** Although advances in proprietary imaging and noise-reduction technology have enabled ultra-portable X-ray systems to capture high-quality images using low-dose radiation, local radiation safety rules should be followed to obtain high quality images with the least amount of radiation. Precautions are needed to ensure the safety of healthcare workers and patients, especially when deployed in the field. For example, an X-ray screening camp should be set up in a non-residential location, barricading areas with exposure risk, and making sure that unauthorized people do not stray any closer to the detector area than remains safe, among other radiation safety measures as required by the local radiation regulatory agency.

Further, sites should be assessed for suitability for mounting the detector in terms of **privacy** for patients who need to remove any clothing with metallic components, or accessories, before taking a CXR.

Section 4.6 Data Privacy and Security

Most countries in the world have data protection or privacy laws that regulate data privacy and security. Data privacy and security are interdependent concepts. Data privacy involves the right to restrict the use, access, disclosure, and dissemination of personal information. Meanwhile, data security comprises technological and non-technological mechanisms that limit access to personal information, its use, access, disclosure and dissemination of information.

Country programmes and implementers of CAD technology should take steps to ensure the privacy and security of patient data when using CAD software. This will entail legal, technical, and operational measures to safeguard the collection, storage, and processing of data. This section discusses how to protect the privacy and security of digital data in AI projects while ensuring the benefits such projects deliver.

Data privacy and security are clearly essential to protect the human rights of people affected by TB and others who provide their personal health data for processing using CAD technologies. Although this is of fundamental importance, it need not present a problematic hurdle. Safeguarding data privacy and security can and should be achieved without interfering with the use and functioning of CAD technologies. Implementers can use and benefit to the full from CAD technologies while keeping digital data private and secure.

Data Ownership

Establishing ownership of digital data is critically important for data privacy and security. For the CAD products in the GDF catalog, the principal contractual agreement with CAD suppliers stipulates that the implementers and country programmes who purchased CAD technology through GDF retain **full ownership** at all times of any data collected using CAD. This ensures that implementers retain ownership of their data even after the CAD supplier analyzes and modifies the data in online (cloud) and hybrid deployment modes (Chapter 2). CAD users who procure equipment independently of GDF should establish clear data ownership in the principal service agreement with a CAD supplier.

Restricted Data Use

Restricting the use of digital data to a limited set of purposes associated with CAD technologies is essential for data privacy and security. The principal agreement with the CAD suppliers in the GDF catalog stipulates that CAD suppliers may only use implementers' data to provide offered CAD services – i.e., to read CXR images and provide a numerical abnormality score, a heatmap, or other related information. No other use, such as further training or optimizing CAD products is permitted unless the supplier obtains the explicit, written consent of CAD users purchasing through GDF, and only for an additional limited and specific purpose. Other CAD users who procure outside GDF are encouraged to establish clear data usage clauses in the principal service agreement with a CAD supplier.

As mentioned above, CAD users purchasing through GDF retain full ownership of all data (in digital or other forms) that are received or processed through the technology. They may therefore use that data themselves for any other purpose necessary, such as research or programme monitoring and evaluation, provided that in so doing they do not contravene any legal, ethical, or other obligations towards the individuals whose personal health data they collect. The Stop TB Partnership encourages CAD users to seek legal advice if a CAD supplier uses or attempts to use data for purposes that exceed the contracted services without explicit written consent.

Data Processing Agreement

Data processing agreements (DPAs) are contracts that outline the legal roles and responsibilities of parties involved in the transfer, storage, and processing of personal data. The overarching aim of DPAs is to ensure the privacy and security of personal data in accordance with the law while facilitating the free flow of information for commercial and other purposes.

DPAs are relevant to both the party that shares its data for processing (i.e., the data controller [implementer]) and the party that receives and processes the data (i.e., the data processor [CAD supplier]). DPAs are required under the European Union (EU) law on data privacy and security – the General Data Privacy Regulation (GDPR) – which provides a global standard for data protection. CAD suppliers based in the EU (Delft Imaging Systems, for example) must use a DPA. However, organizations worldwide may also use DPAs for data protection. Implementers who are not subject to the GDPR may choose to use DPAs to simply establish their obligations, under local laws, and those of the CAD supplier processing the data collected. As such, DPAs function to uphold the rights of the individuals served by an intervention.

The Stop TB Partnership has created a DPA template (here) for CAD implementers- with brief advice on how to use it (here) -modelled on standard contractual clauses under the EU GDPR and designed to maximize users' data protection. Among other things, the DPA template:

- Protects the confidentiality of the CAD implementer's data;
- Requires the CAD supplier to implement appropriate technical and organizational measures to ensure the confidentiality, security, and integrity of the CAD implementer's data;
- Compels the CAD supplier to delete or return all the CAD implementer's data upon request of the user or at the end of the provision of the CAD services;
- Obligates the CAD supplier to assist the CAD implementer in responding to enquiries and requests made by data subjects, such as patients, regarding their personal data, including those arising from local law; and
- Requires the CAD supplier to obtain prior authorization from the CAD implementer upon reasonable advance notice before engaging third parties to process the user's data, such as contracting a supplier to store the implementer's data in a commercial cloud.

Notably, the contractual agreement between the GDF and CAD supplier legally compels CAD suppliers to enter into a DPA with each CAD user purchasing through GDF. In some countries, this will involve multiple CAD users signing a DPA with a single CAD supplier, such as when a central authority purchases CAD devices and distributes them for use in different clinics. Modifications to the DPA template may be required under local law and should be done in consultation with a lawyer. Changes to the DPA template may also be negotiated with the CAD supplier.

Non-Disclosure Agreement

Non-disclosure agreements (NDAs) (also called confidentiality agreements) are standard contracts used in various settings to legally bind individuals and organizations to secrecy and confidentiality regarding shared information. NDAs can be unilateral or reciprocal. They either bind one or both parties in the agreement, depending on whether both parties share confidential information.

Stop TB Partnership have created a unilateral NDA template for CAD implementers designed to maximize the confidentiality of their data (here), with brief advice on how to use it that can be downloaded here. Among other things, the NDA template:

- Requires the CAD supplier to keep secret and confidential all information the implementer shares with the supplier related to the CAD services, including all CXR and other patient data; and
- Obligates the CAD supplier to return or destroy all the CAD implementer's confidential information – including all copies, data sets, records, and notes of the information – at the end of the services relationship or at any other time upon the implementers' request.

Notably, the contractual agreement between the GDF and CAD supplier legally compels CAD suppliers to enter into an NDA with each CAD user purchasing through GDF.

Sidebar: DPAs and NDAs: what is the difference and why use both?
DPAs and NDAs protect the data shared between a CAD implementer and supplier in different ways. NDAs primarily concern data confidentiality, meaning all data shared with a partner cannot be disclosed further without the consent of the organization to which it belongs. NDAs are often used to maintain an organization's secrets, but also apply to patient data as well as any other information an implementer may share with a CAD developer. Meanwhile, DPAs are more concerned with data security (than confidentiality). They are used to outline the roles and responsibilities of both parties involved. As such, implementers can use a DPA to express how a CAD supplier should use and protect their data, while an NDA is used to ensure confidentiality of all data.
In short, using both ensures both data confidentiality (NDA) and data privacy and security (DPA). For this reason, Stop TB Partnership has obligated both Delft Imaging Systems and Infervision to sign both an NDA and DPA with each CAD implementer purchasing through GDF.

Data De-Identification

CAD implementers may choose to de-identify data from CXRs before sharing it with CAD suppliers for processing and analysis. Data de-identification is the process of removing personally identifiable information (PII) from data so that the identity of the person who provided the data cannot be determined. De-identification is not a single technique but rather a collection of methods, algorithms, and tools that can be applied to different kinds of data resulting in varying levels of protection. The two primary methods to de-identify patient data in a DICOM file are anonymization and pseudonymization.

Anonymization involves removing PII, such as name, age, and gender, from the header elements in a DICOM file or replacing such information with random data to remove all information that could be used to reveal the patient's identity. If the implementation requires that CAD outputs are linked with other databases, such as electronic laboratory registers, a unique patient identifier (ID) system should be used. If a unique patient ID system is employed, its integrity must be maintained: the ID must not therefore be removed or modified.

Pseudonymization is a process by which personal data is modified so that it can no longer be attributed to a specific individual without the use of additional information, which is kept separately and securely. Pseudonymizing a DICOM file involves replacing the PII in the file, such as name, age, and gender, with one or more artificial identifiers that can, if necessary, be used by authorized personnel to re-identify the patient.

Anonymization provides greater data privacy and security than pseudonymization but, in theory, prevents the re-identification of patients from the anonymized data. By contrast,

pseudonymization still offers meaningful data protection while allowing for the re-identification of patients from pseudonymized data.

The Stop TB Partnership recommends using a unique patient ID system whether or not de-identification is envisaged, especially when interoperability between information systems is important. Implementers wishing to de-identify patient data should set up their de-identification script with the assistance of an IT specialist in collaboration with the CAD supplier's engineer.

Section 4.7 Installation

The installation process is mostly managed by the suppliers, but it is strongly recommended that a **project IT specialist** (system, application, or network engineer) is present to collaborate with the supplier's engineer.

The following should be borne in mind:

If CAD software is not already in the package with the X-ray system, it is advisable to keep the **X-ray system supplier's** engineer informed and reachable during installation of CAD software.

Local Area Network (LAN) is required if CAD software is installed on a different computer from the one linked with the CXR machine used for screening (two-device mode). A network connection is then required to transmit digital CXR copies from the X-ray system workstation to the CAD laptop. A **static IP address** should be assigned to both computers so that a DICOM node for image transfer can be set up on the X-ray system workstation to ensure transmission of images to the CAD laptop.

- Remote access, through applications such as TeamViewer, or AnyDesk, should be granted to CAD suppliers at time of deployment and for maintenance and troubleshooting. Some intranets prohibit remote access applications: this should be discussed and resolved with the site administrator.
- Administrator rights might be preferred or required by some CAD suppliers during installation, maintenance and troubleshooting when remote access is granted.
- Third-party software should not be installed on the dedicated CAD laptop without first consulting the CAD supplier, otherwise a system crash (failure) could ensue.

1

Section 4.8 Training and Capacity Building

In order to raise awareness of the far-reaching potential of these products, a training programme should be planned and delivered. This will aid successful adoption of CAD technology and ensure the sustainability and scale-up of CAD interventions.

There is significant variation in technical specifications, hardware, and software requirements for installing, running, and maintaining the CAD software. As a result, X-ray system manufacturers and CAD developers provide training and resources for relevant project personnel on the proper use of their product specifically, including:

1. **On boarding training**: on safety, installation, assembly, and operation, including familiarization with the software interfaces.
2. **User manual:** covering installation, software updates, troubleshooting and maintenance.
3. **Onboarding toolkit:** covering IT, infrastructure, and human resource requirements.

This product-specific training can be usefully supplemented with targeted training on CAD in general, to give a broader range of stakeholders an overall understanding of CAD. Although most of the following training sessions will be designed primarily for implementers and technical staff, there is no reason why administrative NTP leadership, responsible for approving policy and finance, should not be invited to some or all of them. Topics could include: a detailed presentation of products, product use-cases, software administration and utilization, validation studies, relevant testimonials and publications, as well as education on threshold selection, and the public health impact of CAD technology. This section provides a starting point for identifying training needs, stakeholders to be trained, suggested training curricula, and training tools for a CAD project.

Training Plan

The first step of any training programme is to create a plan for acquiring, developing and disseminating the necessary training materials, including prescribed user manuals for both technologies, technical documentation (e.g., data dictionaries) and maintenance manuals. A training plan should also identify who requires training and what strategies will be used.

All training content needs to be translated or adapted to the local context. As the use of X-ray technology in the diagnosis and screening of TB is already widely understood in principle, digital training tools like short videos and animated manuals could be explored; online tools will accelerate the dissemination of information.

Stakeholders to be trained

Stakeholders should be identified to receive tailored training based on their role in the project. These can include:

Governmental bodies, including:

- National TB Programmes (NTP)
- Ministry of Health
- Medicines and Medical Devices Agency
- National Centre for Personal Data Protection (or equivalent)
- University, teaching hospital

Medical practitioners and professional associations, including:

- Pulmonologists, chest specialists, radiologists, informal medical practitioners, biomedical engineers and nurses

- National TB Association / Society
- National Radiography and Radiology Associations (or equivalent).
- National Medical Association (or equivalent)

In-country implementers, including:

- Principal local implementing partners
- Local NGOs involved in active case finding (ACF)
- Primary Healthcare Facilities
- Community Healthcare Workers
- TB-affected Community Organizations

Local communities, including:

- Patient groups
- TB-affected community organizations
- Partnerships between NGOs and Community-based Organizations

Training curriculum

Supplementary training – in addition to any provided by the manufacturer –should be used to reinforce technical understanding of CAD and help to place it firmly in the programmatic setting. A training curriculum can be designed by the relevant project or programme manager. The expertise of educational specialists could usefully inform the design of a curriculum covering any or all of the following topics:

1. What is CAD (and the underlying AI technology, deep learning neural networks)?
2. How has the application of CAD technology evolved?
3. What is the role of CAD technology in TB screening and diagnosis?
4. What CAD products are available for TB?
5. Where does CAD technology fit into the diagnostic algorithm?
6. How do you interpret a detailed evaluation of updated or new CAD software?
7. What is required for CAD implementation: general input, server, hardware, and other requirements?
8. How do you decide on a threshold score?
9. What happens first, before the software can work (server, validation, installation)?
10. M&E (monitoring and evaluation) and indicators for the adoption of technology (described in detail in Section 4.9):
    a. Number of people screened for TB using X-ray and CAD for diagnosis.
    b. CAD threshold score used to determine positivity.
    c. Positivity rate of chest X-ray and CAD at implementation sites.
    d. Percentage of people screened positive for TB with X-ray and CAD who were referred for confirmatory testing.
    e. Positivity rate of confirmatory test (e.g., Truenat or Xpert) for people screened positive for TB with X-ray and CAD.
    f. Percentage of people screened positive for TB with X-ray and CAD/AI who were diagnosed without bacteriologically confirmed TB (clinical diagnosis).

Training content should be tailored to the stakeholder's role in the CAD project. A training matrix based on the above curriculum is provided below to help target content to different audiences (Table 14).

Table 14. Training Matrix

Key Stakeholder	Content from above curriculum	Training tool(s)	Frequency of training
In-country implementers, national and international partners			
Principal local implementing partners	All 10 components	Training Manual	Onboarding and repeat yearly if possible
Local NGOs involved in ACF	All 10 components	Training Manual	Onboarding and repeat yearly if possible
Primary Healthcare Facilities	Components 3 to 8	Short, animated videos or printed job aids	Onboarding only
Community screening workers	Components 6 and 7 – Special care should be taken to explain that there is no change to the process for referral and for taking X-rays	Short, animated videos or printed job aids	Onboarding and repeat yearly if possible
X ray facility (radiographer, radiologist, chest physicians)	Components 3 to 8	Presentations, short videos explaining installation and maintenance, troubleshooting	Onboarding
TB-affected community organizations and patients	Components 1 to 3. Emphasis on reduction of time taken for diagnosis, accelerated links to care, and non-invasive nature	Patient communication material and information by health worker or prescribing physician	On presentation to screening site
Governmental bodies	All components except 10	Printed manual and/or short videos	Onboarding only
Medical practitioners and professional associations	All components except 10	Printed manual and/or short videos	As software updated or new features are added

As a result of training, understanding of the technology and its role in TB control should be improved for all stakeholders. Training may also be used to address the queries and concerns particular to groups such as people with TB, and national radiology or medical associations. In addition to the above, health workers with a hands-on involvement with the CAD software should also receive practical training from the supplier on operation, reading, and output interpretation.

Additionally, standard operating procedures (SOPs) for using CAD technology may be developed. SOPs will be developed by involving a broad range of specialists (radiologists, pneumologists, IT and/or biomedical engineers) and should be consulted within the technical

working groups at the NTP level. SOPs should derive from current international evidence on using CAD technology but adjusted to the local context and local experience (if any). They should be regularly updated based on emerging needs and the recommendations of international agencies. SOPs should be regularly updated at a frequency determined at the country level.

Section 4.9 Monitoring and Evaluation

Monitoring and evaluation (M&E) will serve to track progress during the piloting and roll-out phases of the project. This should identify any need for technical modification or maintenance. In due course, M&E should demonstrate the impact of the new approach on TB case detection and other health-related outcomes. A data register must be developed to capture CXR data, and CAD software should be calibrated, such that outputs are sent directly to the relevant recording and reporting system. A unique patient identifier component will probably be needed to link CXR data with subsequent confirmatory (laboratory) data.

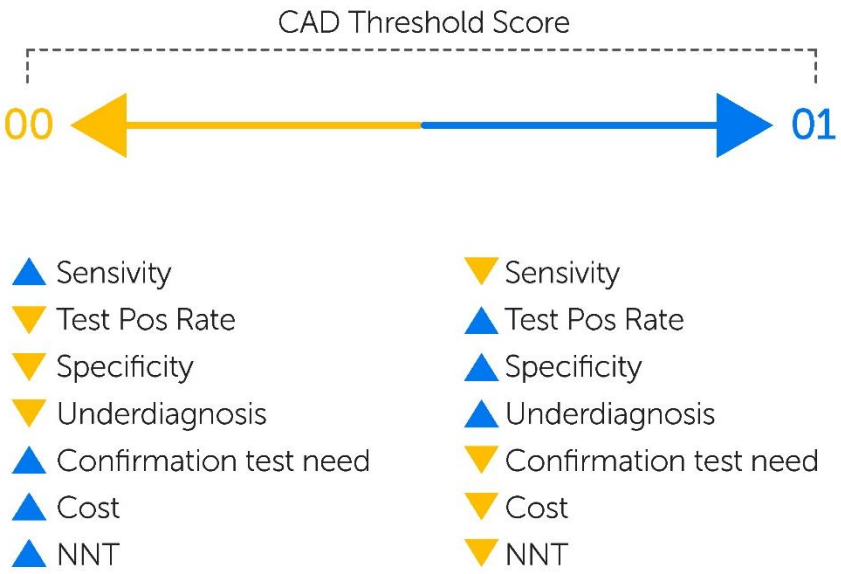
Indicators selected should be: 1) process-oriented, evaluating the performance of the solution during roll-out and maintenance; and 2) impact-oriented, evaluating the impact of the solution on case finding and other health outcomes, as well as programme targets. A list of proposed indicators is shown in Annex 8. These should be adapted to match country circumstances and the target audience.

Chapter 5. Threshold Score Selection Strategies

CAD software processes a chest X-ray image by generating an abnormality score anywhere between zero (or 0%) and one (100%). This number represents the machine-generated likelihood of an abnormality suggestive of TB being present. This score represents – but is not linearly associated with – the continuum from a vanishingly slight chance to a near certainty of TB-related abnormalities being present. The raw number is of little use to healthcare workers until an appropriate threshold score has been selected – then the software can begin to contribute meaningfully to the clinical process. This step converts the number into a clinical suggestion as to whether confirmatory testing is advised or not, expressed, for example, as "TB abnormalities present – confirmation TEST REQUIRED" or, conversely, "TB abnormalities absent – confirmation TEST NOT REQUIRED".

The ability to choose among threshold scores give users the flexibility to target divergent programme goals. Under certain circumstances, a **higher threshold score** will be selected, resulting in **higher specificity, but lower sensitivity**. This means the test positive rate (proportion of people testing positive on confirmatory tests) will increase, and fewer confirmation tests will be needed. In other words, the number of people needed to test (NNT) will decrease, and therefore **testing costs will be lower**. However, more **people with TB will be missed** (that is, fail to receive a diagnosis because they had a score below the threshold). Under different circumstances, when the priority is to find more TB patients (and when there are fewer constraints on resources or testing capacity) CAD implementers can choose a **lower threshold score**, resulting in **lower specificity, but higher sensitivity** (Figure 8)**.**

Figure 8 The implications of CAD threshold score selection



The selection of a threshold score is clearly of vital importance. However, selecting an appropriate threshold score is often described by early implementers as one of the chief initial challenges. It is not possible to set up a universal threshold score because every CAD software product is constructed differently. A neural network does not resemble a standard statistical method so the distribution of abnormality scores cannot be described as any common statistical distribution patterns. (Section 1.4). As such, local data from the target

population is almost always required for analysis (an on-site calibration study) to identify the optimal threshold score for that particular setting.

This chapter presents four strategies for the collection of local data that will underpin threshold score selection (Section 5.1). It then presents a framework (derived from the literature) for analysis of that data (Section 5.2).

Because the search for an optimal threshold score with adequate scientific rigor is a complex process, implementers are encouraged to seek the assistance of a specialist who is familiar with the scientific and technical challenges involved.

Section 5.1. Setting a Threshold Score for the Local Context: Data Collection Strategies

The critical step in selecting an appropriate threshold score is the collection of local data from the targeted population in a specific setting. The data should include original chest X-rays alongside the corresponding demographic and clinical data. In aggregate, this data should mirror – or closely resemble – that of the target population. Therefore, patient data from TB clinics, for example, would be of little use in a calibration study intended for community-based screening. There are several alternative strategies for the collection of appropriate local data for threshold score analysis. Not all of these approaches are scientifically rigorous or based on optimal data. Generally, there is a tradeoff between the complexity of the method and the accuracy of the selection. Depending on the resource and capacity constraints, practical compromises using suboptimal data can be unavoidable.

Comprehensive operational research

WHO and the Special Programme for Research and Training in Tropical Diseases (TDR) developed a toolkit providing step-by-step guidance on how to design and conduct operational research geared towards selection of a local threshold score.[5] Depending on access to imagery and metadata from both confirmed TB patients and non-TB patients, operational research can be retrospective or prospective. The toolkit can be accessed from this website.

However, if access to existing data is limited and prospective research is needed to generate new data, this strategy will demand substantial research capacity and resources. In a low prevalence setting, many healthy individuals will have to be screened and tested by confirmatory diagnostic tests, driving costs up accordingly. If the time and resources are not immediately available for a rigorous undertaking on this scale, it might instead be better to opt for the next two strategies outlined below.

Iterative operating point calibration (ITSC)

Researchers at Google and the Stop TB Partnership have designed this approach to help make threshold score selection more efficient. ITSC starts with a rough threshold score (either based on current literature, or simply the one-size-fits-all value recommended by the manufacturer). This is then refined through iterative cycles of data analysis and threshold modification until programmatic targets are reached.

By providing the opportunity to refine the threshold score in parallel to an ongoing intervention, ITSC is suitable for sites where time and resources do not allow for suitably rigorous research (above) at the outset of an intervention. Refining threshold to a maximum over several iterations is likely to be better than continued operation using a threshold chosen based on suboptimal data.

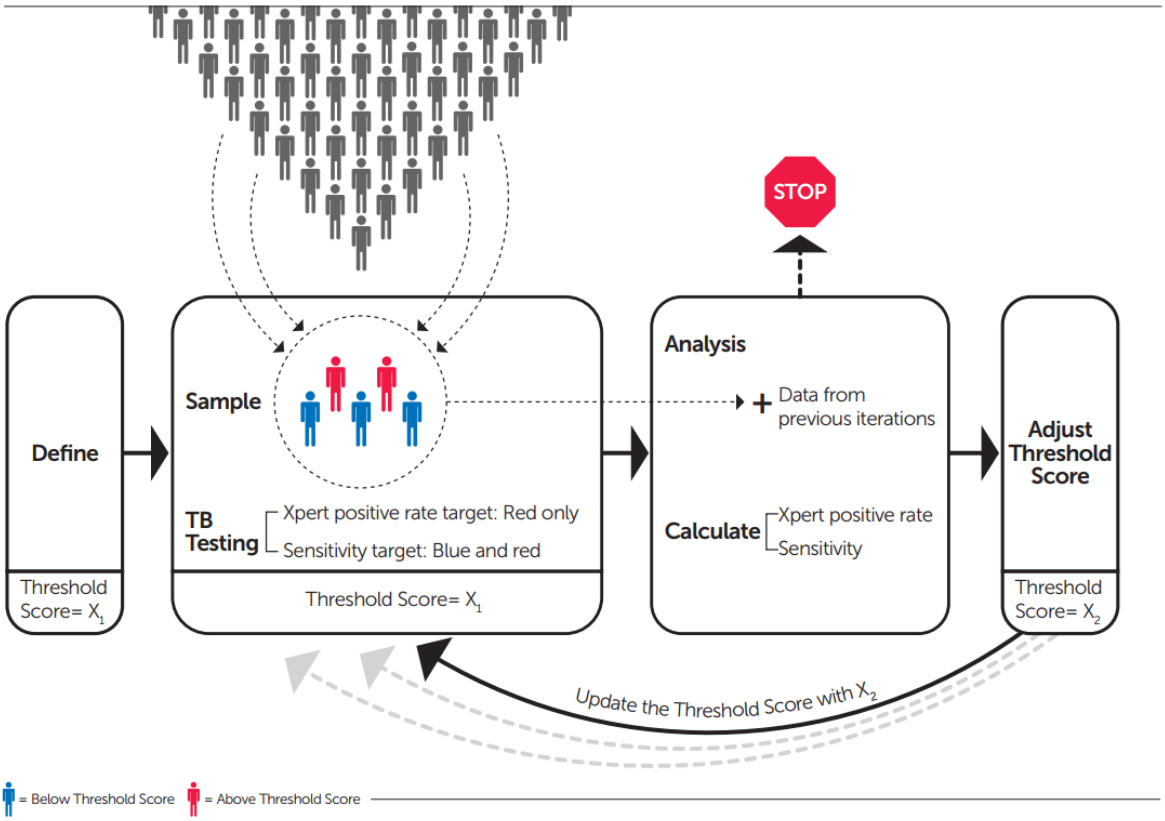


Figure 9 The conceptual framework behind the ITSC strategy

Before implementers begin to collect data, they must not only choose an initial threshold score as described above, but also define the goal value (programmatic target) which the modified threshold will be modified to achieve in due course. That value could be a target sensitivity and specificity, or a proportion of confirmatory tests to save. Now implementers can begin the first iteration by sampling a proportion of their intervention population whose X-rays are read by CAD and who are called back for confirmatory testing. The goal value will determine whether confirmatory test results are required from all individuals or just those with an abnormality score above the threshold (details, Annex 9).

As soon as all test result results are available, the Xpert positive rate and the sensitivity of CAD is calculated for all individuals sampled. The threshold score should then be adjusted informed by the analysis. After this, the next iteration can begin with a new sample which is pooled with that from the previous iterations in the analysis. Thus, the threshold score is progressively adjusted, using the combined “learning” of all previous iterations, until the target value is achieved (see Figure 9).

A detailed step-by-step description of this method is provided in Annex 9 for those with specialist understanding of statistical techniques. Google and the Stop TB Partnership are currently working on an online platform to help analyze iterative data collected and perform hypothesis testing. Final work will be published on the Stop TB Partnership’s Digital Health Technology (DHT) Hub.

Reactive Adjustment

This adjustment strategy allows for a rapid and flexible response to undesirable indicators. First of all, an initial threshold score is selected on the basis of similar experience, existing publications, or supplier’s recommendation, as per the ITSC strategy above, but there the

similarity ends. There can be several types of undesirable indicator that can arise. One might be a considerable number of patients with a score lower than the initial threshold scores but who are nevertheless found to have TB. Another undesirable indicator might be a low positive confirmation test rate.

When using this strategy, implementers allow themselves greater flexibility with regard to the threshold score, such that people with a CAD score lower than the initial threshold score – but with other signs of TB – still undergo microbiological testing or have their CXRs read by a radiologist. A 0.05 to 0.1 downward adjustment of the threshold score can be made if a considerable number of false negatives occurs. An upward adjustment can be made to achieve a higher positive confirmation test rate.

Set and forget

There are clear caveats to this third strategy, so it cannot generally be recommended. As the pithy name suggests, a threshold score is selected and employed for the duration of the programme. Again, the threshold score could be selected on the basis of various factors, including prior experience, the literature more broadly, or the supplier's recommendation. There is a growing volume of CAD literature which reports sensitivity and specificity over the entire continuum of abnormality scores (often published when a new software version is released). A strategy reliant on these figures has to rest on the optimistic assumption that CAD performance will be similar in the relevant intervention population. In its defense – perhaps as a practical compromise – it could be noted that the strategy would indeed work well enough if the intervention population happened to resemble the population that gave rise to the manufacturer recommended score in the first place.

Section 5.2. How to Analyze the Data?

The local data collected should be analyzed in combination with the desired programmatic goals. Different programmatic goals require different threshold scores. For example, a large active case finding (ACF) programme is usually limited by the number of confirmation tests provided for by the project budget. Conversely, CAD technology deployed in an immigration screening setting will require a very high sensitivity.

Selection of a threshold score will be driven by several factors, among which the following are arguably the most important:

- Accuracy: sensitivity and specificity
- Cost-efficiency
- Test positive rate
- Confirmation test capacity

A *decision analysis framework* can be used to analyze and monitor the accuracy and programmatic implications of CAD software over a continuum, enabling re-tuning of the calibration of the threshold score in the intervention setting for a specific programmatic requirement.

This decision analysis framework incorporates important indications of relevance to implementation, such as confirmation tests saved and NNT, to quantify cost-effectiveness and the ability to triage.[13] Under this framework, CAD software is evaluated in a hypothetical population, using an assumed triage process whereby the abnormality score serves to triage all individuals in the study population for confirmatory follow-on diagnosis (Xpert) by means of a predetermined threshold score. The proportion of subsequent Xpert assays saved (with 0% representing the Xpert testing-for-all scenario) is then calculated as a proxy for the cost-effectiveness of the software under consideration. Likewise, the NNT is used as a proxy for the software's ability to triage. This framework evaluates the trade-off among sensitivity, the proportion of confirmation tests saved, and the NNT over the complete range of abnormality scores.

How to use the framework?

Figure 10 shows an example application of the framework based on a study in Bangladesh,[13] which modelled the results of five commercial software products (CAD4TB (v7), InferRead DR Chest (v2), Lunit INSIGHT CXR (v4.9.0), JF CXR-1 (v2), and qXR (v3), using this framework in a hypothetical population.[13]

The top graph plots the sensitivity of each CAD software product across all abnormality scores between zero and one. The middle graph shows the proportion of Xpert confirmation tests saved across all abnormality scores (such that 0% represents an Xpert testing-for-all scenario while 100% means that nobody receives an Xpert test). The bottom graph shows the NNT across all abnormality scores. The graphs are stacked vertically for ease of comparison so as to aid understanding of the relationship between the three.

These can be read and interpreted to inform threshold selection within a population based on the goals of an intervention.

For example, using the results in the above study population:

- **To select a threshold score:** a threshold score of 0.7 for CAD4TB results in 85% sensitivity, saves 70% Xpert tests, and reduces NNT to 2.2. To obtain the same level of sensitivity, a threshold score of 0.45 for InferRead DR Chest is needed, saving 61% of Xpert tests and reducing the NNT to 3.

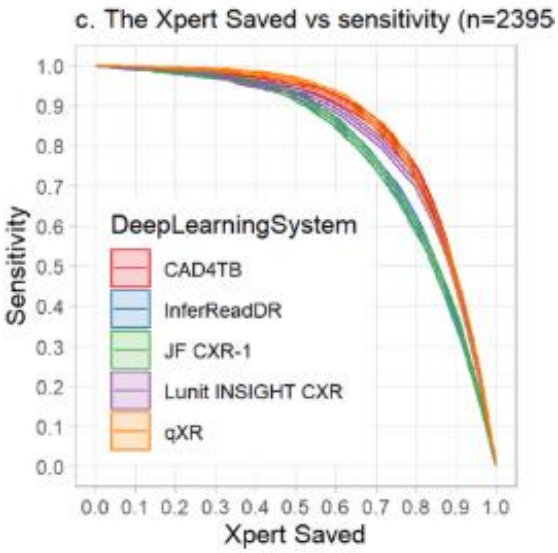


Figure 10 Plots generated by the Decision analysis Framework [13]

- **To identify a high number of TB cases but minimize compromise on Xpert tests saved:** To identify at least 95% of TB positive individuals, CAD4TB would save 51% of confirmatory Xpert tests, while InferRead DR Chest would save 41% of subsequent tests (with 0% representing the Xpert testing-for-all scenario).

- **To stay within budget by reducing Xpert testing but minimize compromise on sensitivity:** Opting to reduce follow-on Xpert testing by 75% results in sensitivities of 79.7% for CAD4TB, and 69.3% for InferRead DR Chest.

Chapter 6. Case Studies

Some early implementers have piloted the use of ultra-portable X-ray systems with CAD technology. We now summarize their diverse experiences using different products, and in so doing recapitulate a few of the points discussed above, to highlight challenges and lessons learned. Further case studies are available in a FIND Technology Landscape Analysis on the subject.[21]

Sidebar: Early Implementation of CAD and Ultra-portable X-ray

The case studies in Chapter 6 were documented through the Stop TB Partnership's network of grantees and CAD developers. All began screening activity using CAD and ultra-portable X-ray during 2020. This is a rapidly developing field, so it should be borne in mind that the products described are in fact earlier versions of those in the GDF catalogue. A particularly notable change is that Fujifilm's FDR Xair generator can now be charged while performing exposures (this overcomes a limitation flagged in some of the case studies). Secondly, all implementations occurred prior to the announcement of the updated WHO guideline on CAD in March 2021, hence the software is used cautiously (with radiologist or clinical supervision, or as a quality assurance tool). With the endorsement of the WHO, CAD will now be used with more confidence.

Childhood TB detection in Zambia

Project dates: July 2020 – present
Local Implementing Organization: Center for Infectious Disease Research in Zambia (CIDRZ)
Interviewees: Dr. Monde Muyoyeta (Project Lead), Dr. S. N. (Study Coordinator, clinician), Dr. Brian Shuma (clinician), and Charles Imbuwa (Radiographer).
Country: Zambia
Project setting: Facility-based TB screening in children in two remote clinics in Lusaka, a region with one of the highest TB burdens in Zambia.
CAD software: CAD4TB
X-ray system: Fujifilm FDR Xair

Hardware and Accessories

Core X-ray System

- Fujifilm FDR Xair
- Detector
- Tripod stand for generator (with rotating arm)
- Tripod stand for detector
- 2 laptops (one included with purchase and one purchased by the project)
- 2 spare batteries for the detector and detector charger
- Solar panel and battery

Accessories

- CAD4TB box
- Hand switch for taking exposures remotely.

Implementation and Operation

- CAD and ultra-lightweight X-ray were used at two facilities in Lusaka, with screenings held every weekday for children (and adults) who arrived at the clinic. CXRs were performed in parallel with symptom screening.
    - On weekends, the FDR Xair was transported to a remote facility in another high-burden TB district that did not have any X-ray resources.
- Since this was a study setting, the field team included a clinically qualified radiographer, a nurse, two research assistants, and 4 community health workers/treatment supporters. Fewer people would be required in routine use.
    - The team was also assisted by a supporting radiographer and a data team (an assistant, a manager, and a senior manager) who were centrally located.
- Young children were screened by having their mothers hold them in position with their chests exposed to the generator and their backs on the detector, with the mothers standing behind the detector.
- Seriously ill patients were screened either sitting or lying down.
- Radiographers and clinicians would judge whether patients should be referred for follow-up confirmatory testing based on their CXR images, symptoms, and CAD output.

Field set-up and configuration

Hardware: CAD4TB was used with an internet connection and was integrated with the Fuji Xair system using a two-device set-up. One laptop (the Console Advance) was dedicated to receiving CXR images from the FDR Xair, which was connected to the CAD4TB box. The second laptop was used to access the CAD4TB results from the web browser (Google Chrome), since the Fujifilm Console Advance could not support Google Chrome to connect to the Delft CAD4TB cloud.

Internet requirement: CAD4TB was used both with and without internet connection (**hybrid**). The internet was used to upload CXRs for processing on the CAD4TB cloud, these could then be accessed on the CAD computer by logging in to an online platform. **When internet connection was not available**, the CAD4TB box could still be used, provided the system was connected on the same LAN. The CXRs could then be uploaded to the cloud when the internet connection was restored.

Integration with PACS: There was not a need to integrate CAD4TB with a national PACS, but this may change in the near future.

Daily set-up required installing the detector and the generator on their respective stands and aligning them. Overall, this took approximately 10-15 minutes.

Integration between CAD and the X-ray machine

Integration was achieved smoothly by the project's IT team with engineers from both Delft Imaging Systems and Fujifilm. The second laptop was required to integrate the two systems, since the Fujifilm laptop could not support Google Chrome to connect to the Delft CAD4TB cloud.

CAD validation was not performed since the team had prior experience with CAD4TB.

Threshold score selection

A **threshold score** was not defined for this project since it focused on assessing CAD abnormality score accuracy in children. Usually, the project

team selected a threshold score based on prior experience and the data they collected while using CAD in previous projects.

Key Implementation Considerations

Electricity and power

Battery life: The generator's battery lasted for 20-25 exposures. The generator was subsequently replaced; however, the new generator still generated only a maximum of 30 exposures on one charge while operating on the recommended power settings. Spare detector batteries were also provided and could be exchanged in the field to prolong operation.

Supplementary power sources: The project was given a solar panel and a battery to provide additional charging for the generator between exposures in the event of power outages in the field. Consequently, TB screening could last for a whole day.

Portability

- Although the Xair system was mostly used in facilities, it was also regularly moved between two project clinics.
- The FDR Xair generator, the detector, and the laptops all fit into a robust carrying case. This case could be both carried and wheeled, and it was light enough for a single person to lift. Besides the case, the generator tripod and the detector stand had to be carried by hand.
- For ease, two people were deemed best for carrying all the equipment; however, one person could manage if need be.

Figure 11. The packaging of (a) the generator and accessories, (b) the detector, and (c) the carrying case (external). *Images courtesy of CIDRZ.*

Radiation Safety

- X-rays were conducted with standard safety measures, even though the local authority had confirmed that a lower radiation dose was emitted by the FDR Xair.
- The **radiographe**r was either behind a lead wall while taking the exposures using a hand-switch or wore a lead apron while in the room with the patient. The radiographer wore a radiation badge that was checked twice a year for radiation exposure.
- **The facilities** were organized so that exposures would occur in an isolated room and included signs with warning symbols for illiterate patients. These measures ensured waiting patients were not exposed to scatter radiation.

Regulation

- The primary requisite operating permissions were obtained from the Radiation Protection Authority in Zambia. Additionally, the NTP was informed of the project's plans to procure the ultra-lightweight CXR device.
- Permission to import the device was granted based on the equipment's dosimeter. Subsequent operating permits required an assessment of the project site and set-up. The regulatory body concluded that the device was safe to use in a mobile setting (in a room without lead lining), provided that the project followed radiation safety precautions.

Training, service, and maintenance

Online training was provided by Fujifilm's South African team soon after the X-ray machine arrived in Zambia . The two-day interactive training explained how to set up the equipment and operate it. After the training session, the project team had no difficulty operating the equipment and no follow-up training was required.

Technical support was provided by the manufacturer**.** The project staff stated that operational issues were resolved on the same day. Fujifilm also had a **local distributor** in Zambia, which increased the level of service. For example, when the low battery life became an issue, Fujifilm sent local engineers to assess the problem on-site.

Highlights

- The CAD4TB's cloud service allowed centrally located radiologists and clinicians to easily consult with one another via the internet regarding any given CXR. This consultation was made possible by the field team providing the CXR identifier to remotely located colleagues so that they could log into and view the CXR on the cloud platform.

- The image quality was as good, if not better, than stationary X-rays used in the past. The quality was further improved by the Xair system's image optimization software tools.

- The system's portability allowed the team to use it to support TB screening at an additional facility that was located in a different region that had limited x-ray capabilities.

Challenges

CAD

- When the internet was unavailable, it delayed uploading to the cloud, this complicated data retrieval. This limitation resulted in some missing CAD scores in the project records.

Ultra-lightweight X-ray

- Low battery capacity meant that the project had to pause operations to recharge the generator.

- The generator tripod stand was difficult to manoeuvre while taking CXRs of sick patients and children.

- The occasional loss of connection of the console's wireless transmitter caused a delayed or failed uploading of the FDR Xair images to the laptop for review by the clinician.
- The FDR Xair dedicated laptop crashed during Google Chrome installation. As a result, all the equipment had to be returned to Japan for recalibration. This process delayed the TB screening. Broadly speaking, the Xair laptop was not meant to install any software besides the one provided with the generator.

Active Case Finding in Remote Communities in Nigeria

Project dates: 30th November 2020 – present

Local Implementing Organization: KNCV Nigeria
Interviewees: Dr. Eze Chukwu (Project Coordinator), Dr. Bethrand Odume (Executive Director) and Austin Ihesie (Senior Programme Manager, Akwa Ibom Cluster).
Country: Nigeria
Project setting: Hard-to-reach communities in Akwa Ibom and Cross River states.
CAD software: CAD4TB version 6
X-ray system: 1x Delft Light System

Hardware and Accessories

Core X-ray system

- Ultra-portable Delft Light System Backpack Model: BLD34L.
- 1 battery-operated generator
- 1 flat panel detector
- 2 computers:
  - CAD4TB laptop: HP EliteBook
  - Console tablet: Microsoft Surface tablet
- 1 detector stand
- 1 solar panel
- 2 backup batteries

Accessories

- CAD4TB box
- 1 label printer and barcode scanner
- Link dongle, link cables, router etc.

Implementation and Operation

- The project screened rural and semi-urban populations, including children, who had limited access to healthcare.

- The field team consisted of three people: a coordinator (responsible for advocacy, engagement, site assessment, etc.), a radiographer (who operated the Delft Light), and a data clerk (responsible for logistics and data management).
- The project used one X-ray system and screened an average of 90 people daily. The screening camps operated every day except weekends.
- CXR screening was used in parallel with symptom screening.
- **Diagnostic decisions** were made using the CAD score as well as a clinician's interpretation and judgement. For example, if people had a score below 60 but still exhibited signs or symptoms of TB, they were further tested using Xpert. Clinicians also read images to make triage decisions when individuals had TB symptoms but low scores.

Field set-up and configuration

Hardware: Ultra-lightweight CXR generator and detector panel connected to two computers: a Microsoft Surface tablet displaying CXR and HP EliteBook displaying CAD4TB results. CXRs were transmitted from the X-ray workstation to the CAD4TB laptop, attached to the CAD4TB box, which transmitted images to the server for analysis.

Internet requirement: Hybrid mode with two devices and a CAD4TB box: some field locations had no internet access, even though the router is attached to the system. In this case, CAD reading was performed offline by the CAD4TB box, and data stored and uploaded to the server when the internet connection was restored.

Data storage: Delft Imaging Systems provided a cloud server and arranged in advance that CXR would be **anonymized** before upload to the cloud.

Integration with PACS: Not undertaken (not needed).

Daily set-up took approximately 30-35 minutes after identifying a suitable field site, with one person setting up the detector and stand, and the radiographer preparing the generator. A further 35-40 minutes was required to tidy up and clean the equipment after a screening session.

Integration between CAD software and X-ray system

Pre-integrated: Since both the CAD software and X-ray system are produced by Delft Imaging systems, the Delft Light package arrived with the CAD4TB installed on the CAD4TB box. Only assembly of the parts was required to begin operation.

CAD validation was not performed because the team had used CAD4TB previously.

Threshold Score Selection

Threshold score of 60 was used to triage patients. This threshold score was determined through previous experience. When CAD4TB was used in mobile vans with a cut-off score of 40, it resulted in a low number of those undergoing subsequent diagnostic testing being confirmed with TB. Learning from this, a threshold score of 60 was used to improve the number of detected cases.

Key Implementation Considerations

Electricity and Power

Battery life: The generator battery can last the entire duration of the operation without recharging. The detector batteries were exchangeable, which helped prolong the operation.

Supplementary power sources, including a power bank and a solar panel, were used so that the system's battery life was seven hours and thus sufficient for a full day of operation (around 80 exposures). A solar panel was originally used, but it was replaced by a power bank due to the difficulties and deficiencies of charging by sunlight.

Portability

- System weight, including its requisite accessories, was estimated to be more than 70kg.
- The detector panel, generator, and detector batteries fit into a backpack. The power station, detector stand, laptops, external batteries, supplementary chargers, and cables had to be transported separately.
- Transport of the entire unit required at least two people.

Radiation Safety

- Despite the reduced power output of the Delft Light generator, local radiation safety regulations were complied with.
- The radiographer wore a lead radiation jacket and neck collar, and used a hand switch to maintain a safe distance when taking exposures.
- Screening was set up in a location far from residential areas, barricading places with an exposure risk, and ensuring no one went within 10m of the detector area.

Regulation

An approval for a previous project by the nuclear regulatory agency was extended to include this project.

Training, Service, and Maintenance

Online training was provided by Delft Imaging for installation and implementation. Training by phone also occurred during field work on topics such as interpreting inverted images and negative CAD scores.

Remote technical support was also provided during installation, and for troubleshooting as needed.

Highlights

- Image quality was described as very good.
- The Delft Light generator battery was highly durable and would allow for 120-150 exposures in the field without going flat.
- Programme staff concluded that the CAD software processed images rapidly and reliably: this helped to triage patients quickly while reducing inter- and intra-reader variability.

Challenges

- The supplier's online training was considered inefficient. Assembling the system took too long for a radiographer unfamiliar with this type of system. Consequently, ad hoc remote technical support was needed several times.
- There were occasional interruptions to when transferring the CXR image from the generator to the CAD laptop.
- There were faults in the built-in generator batteries, which required replacement.
- It was usually necessary to have extra cables and the dongles regrooved since the machine operators were in remote locations and it was difficult to find replacements.
- The equipment was not very portable: the weight of the complete system and accessories was approximately 70kg, and it was logistically difficult for one person to operate it.
- The CAD4TB laptop battery drained quickly.

Detecting TB in Coal Miners in Pakistan

Project dates: August 2020 – present
Local Implementing Organization: DOPASI Organization for Sustainable Development
Interviewee: Dr. Kinz-Ul-Eman (Project Director)
Country: Pakistan
Project setting: Remote community screening (miners and mining communities) in Punjab, Sindh, and Khyber Pakhtunkhwa in Pakistan.
CAD software: Lunit INSIGHT CXR
X-ray systems: 1x FDR Xair from Fujifilm. Accessories: foot switch and 2x detector batteries.

Hardware and Accessories

Core X-ray system

- FDR Xair Generator
- Detector panel
- 2 laptops (FDR Xair Console Advance + CAD laptop)
- Generator tripod
- Steel detector frame
- External detector batteries

Accessories

- Generator foot switch (for switching generator between exposure and charging modes).
- Generator hand switch

Implementation and Operation

- CAD software and ultra-lightweight CXRs were used at mobile screening camps outside health facilities.
- An X-ray technician operated the Fujifilm Xair at the screening camps. The District TB Coordinator provided additional support. The number of community health workers depended on the number of people screened at the camps. Usually, two were employed for a 200-person screening camp.
- On average, 46-50 people came through the camp daily. The highest daily total was 316, which occurred during a period when Covid-19 restrictions were relaxed.
- The images from the CXR were interpreted by CAD. The CAD output was subsequently used in a report format that the camp coordinator interpreted to decide who should receive further microbiological confirmatory testing for TB.
    - People with an abnormal CXR who could not produce a sputum sample received a printout of the X-ray and CAD output on butter paper, which they brought to their follow-up visits at nearby health facilities.

Field set-up and configuration

Hardware: the two-device set-up was used, with FDR Xair console advance dedicated to receiving CXR and a second with Lunit INSIGHT CXR installed for analysis of the CXR images. These were connected using an AP adapter.

Internet requirement: CAD was used offline.

Data storage: All data was backed up on two hard drives. Manual backups were taken from the FDR Xair console advance after each screening camp. Batches of CAD reports from the CAD laptop were extracted and stored before deletion to maintain the storage space in the Lunit laptop.

Integration with PACS was not performed because no national PACS system is used.

Daily set-up only required fixing the Xair generator on the tripod, and the detector panel on the detector stand, then switching on the two laptops. This required minimal technical expertise, and took less than five minutes.

Figure 12. Labelled Fujifilm FDR Xair core system. Image courtesy of DOPASI.

Integration between CAD software and X-ray system

Integration initially required connecting both computers on the same network. This was performed by the Fujifilm Pakistan team in connection with the Singapore office. An AP adapter transfers CXR images from the DR Xair console advance to the Lunit INSIGHT computer for analysis.

CAD validation was not required.

Threshold Score Selection

Threshold score was set at the **default** threshold of 0.5, with any CXR with a score above 0.5 being classified as abnormal.

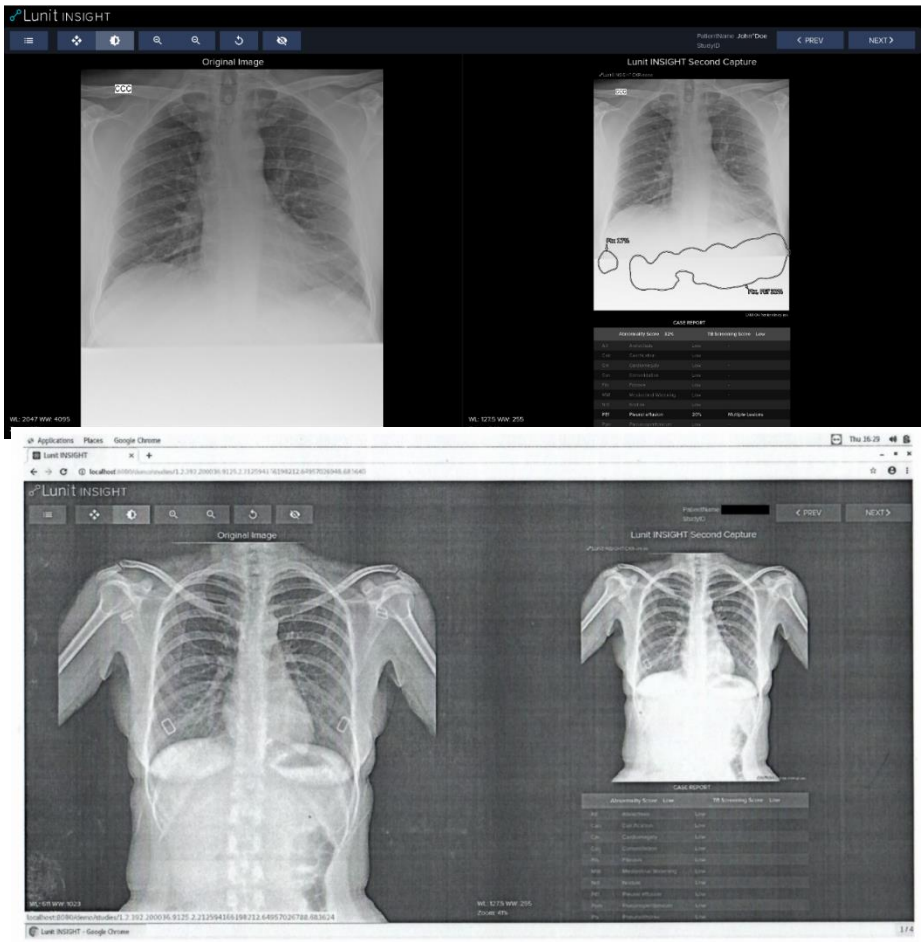


Figure 13: Outputs used by the project. Report output of Lunit INSIGHT CXR (above). Scan of report output printed on butter paper (below). Courtesy of DOPASI.

Key Implementation Considerations

Electricity and Power

- During a typical screening day, four AC power outlets were required for the FDR Xair console advance, the CAD laptop, the detector battery, and the FDR Xair generator through a foot switch.
- **Battery life** was less than indicated by the manufacturer, averaging 35 exposures on one charged battery. The generator could not be charged while taking an exposure, thus a foot switch proved a valuable accessory by enabling easy switching between charging and exposure mode. [As noted, charging can occur at the same time as taking exposures in the new model provided through GDF].
- **Supplementary power sources** included two external detector batteries, however the detector had to be dismantled out of the frame before changing the battery.

Portability

- The generator and detector stands made transport difficult.

    - A steel frame was required to hold the detector panel – this was cut into two parts so that it could be transported more easily.
    - The generator could not be transported fixed to the generator tripod.
- For transporting equipment, the project team used one bag containing the two laptops, and a metal case containing the Xair, tripod and detector console.
- At least three people were required to carry equipment: one person carried a bag containing the two laptops plus the box containing the FDR Xair generator; another person carried the generator tripod and detector; and a third person carried the steel detector stand.

Radiation safety

Though the local radiation authority concluded that the generator produced lower amounts, the device was still operated using safety precautions. The radiographer operated the generator from a distance of 2m using the hand switch while wearing a lead apron and dosimeter.

Regulation

The only approval required was from the Pakistan Nuclear Radiation Authority (PNRA), but this had to be obtained twice: once by Fujifilm to import the FDR Xair system, and once by DOPASI to operate the device. Before granting the operating license, PNRA conducted radiation measurements with a dosimeter from different places. The approval mandated that project X-ray technicians wear a dosimeter on-site that was checked every three months.

Training, service, and maintenance

Training was provided by Fujifilm over two days for both the X-ray system and CAD software. The team had no difficulty using the system thereafter.

Maintenance and technical support were provided by the **local Fujifilm office** under the direction of the Fujifilm Singapore office, which had greater technical expertise.

The inclusion of **component parts exchange** was an important contribution to system maintenance since both the hand switch and the FDR Xair detector required replacement (at different times). The replacement process was rapid and efficient.

Highlights

- The image quality of the FDR Xair was deemed very good by the Head of the Radiology Department at a tertiary hospital in Islamabad.
- The project team felt the portability of the system allowed access to TB diagnosis in a community that would not otherwise be able to access such services.
- The ability of the CAD software to screen for other pulmonary conditions prompted diagnosis of diseases other than TB. The team was also screening for COVID-19 using the same software.

Challenges

CAD software

- The CAD laptop was an older model of substantial size and weight, with limited storage capacity that delayed generating reports.

Ultra-portable X-ray system

- The exposure capacity of the FDR Xair on one full battery charge was approximately one third the number claimed by the manufacturer (35 vs. 100). This number was also limited by the battery capacity of the other equipment, such as the Console Advance, the CAD laptop, and the detector.
- The local Fujifilm office's capacity to provide technical assistance and maintenance was limited, and support issues were frequently referred to the Singapore office.

Watch a video of their screening activities:

https://www.youtube.com/watch?v=4ijbMZCHCT4

Detecting TB in hard-to-reach communities in Vietnam

Project dates: 29 March – 06 April 2021 (8 screening days in a mountainous region), and 09 – 13 April 2021 (5 screening days on an island).
Local Implementing Organization: Friends for International Tuberculosis Relief (FIT).
Interviewees: Vo Nguyen Quang Luan (Head of Country Office) and Andrew Codlin (M&E and Research Director).
Country: Vietnam.
Project setting: Screening in remote settings: island communities (Cu Lao Cham, Quang Nam) and mountainous communities (Phuoc Son, Quang Nam).
CAD software: Lunit INSIGHT CXR.
X-ray system: 1x ultra-portable FDR Xair System by Fujifilm.

Hardware and Accessories

Core X-ray system

- FDR Xair generator
- Detector panel
- 1 Fujifilm FDR Xair laptop
- Generator tripod
- Detector frame

Accessories

- Hand switch (for switching the generator on and off and for charging between exposures).
- Expansion Unit EX-Mobile box (offline Lunit INSIGHT CXR box).
- Power bank

Implementation and operation

- CAD and an ultra-portable CXR were used to screen both island and mountainous populations during the two screening campaigns. Screening was conducted at various locations in the communities, such as pagodas, cultural houses, and primary health facilities (which did not have X-ray services).
- Two or three trained X-ray technicians from the National Lung Hospital operated the X-ray machine, managed the crowds, and recorded the patient information. They were supported by three to five community health workers (depending on the expected throughput), who screened the patients. Large numbers of additional staff were also engaged at the camps as co-screeners for other communicable and non-communicable diseases.
- More than 200 people per day were screened at the camps.
- CAD was used as a quality assurance tool. The CXRs were read by the radiologists, and only a portion of the CXRs were sent to CAD to double-check the radiologists' interpretations.
- The abnormal CXRs detected by the radiologists were printed out and given to the respective individuals, who could then consult on-site pulmonologists.

Field set-up and configuration

- **Hardware:** One laptop was used with the FDR Xair generator and detector. The detector was connected via Bluetooth to the laptop, which was connected in turn via USB to the EX-Mobile box. Both the generator and the detector were used with supporting frames.

- **Internet requirement:** Lunit INSIGHT was used offline with the EX-Mobile box.

- **Data storage:** CXR DICOMs were anonymized and allocated a unique patient identifier before being backed up onto a hard drive at the end of each screening day.

- **Integration with PACS** was not necessary since this was a pilot project.

- **Daily set-up** took 5-10 minutes at most, and only required the aligning of the detector and generator on their respective stands; connecting the detector to the laptop via Bluetooth; and attaching the FDR Xair hand switch to the generator.

Integration between CAD and the X-ray machine

Integration was achieved by connecting the EX-Mobile box to the laptop via USB, and using the Lunit software to display the CAD results.

Threshold score selection

A **threshold score** was not chosen for this project because CAD was not used for triage; rather, the CAD abnormality score was collected.

Key Implementation Considerations

Electricity and power

- **Charging requirements:** The generator's poor battery life limited the screening operations. Replacement batteries for the detector were also needed. The EX-Mobile box was powered by connecting it to the laptop via USB.
- **Battery life** for continuous use was 44 exposures per charged battery.
- A **supplementary power source** (power bank) was procured locally by Fujifilm to extend the battery life.

Portability

- Three carrying cases were used to transport the generator, detector, and their respective stands.
- Portability depended on the hardware set-up. For example, certain types of detector stands were more difficult to transport (such as bed stands where patients could lie down during exposures).
- Though it was possible to have one person carry the system during transport, two were often used for ease.

Radiation safety

- The National Lung Hospital checked the system's radiation exposure before it was transported to the field. The FDR Xair's radiation exposure was lower than stationary devices. Nevertheless, appropriate radiation safety regulations were followed.
- The screening site was set up so that X-rays could be conducted safely, using measures such as maintaining a 3 to 4-meter distance between waiting patients and the generator.

Regulations

The devices required registration for importation and local procurement; this was managed by the local Fujifilm office.

Training, service, and maintenance

- **On-site training** was provided shortly after the system was delivered and set up in the National Lung Hospital.
- Fujifilm also loaned the team an FDR Xair machine while awaiting the approval of the imported devices.
- The team has only operated the device for a short period of time, so maintenance issues have not yet been encountered.

Highlights

- Before the FDR Xair system was deployed, the National Lung Hospital certified that the image quality was good.
- Despite the battery issues, the FDR Xair system was capable of 200 exposures per day using supplementary power sources.
- The handheld X-ray system facilitated outdoor patient screening. This feature was more convenient than using screening trucks, which were not spacious enough to ensure the patient's maneuverability.

Challenges

CAD

- The team observed differences in CAD performance among various CXR machine brands.

Ultra-portable X-ray

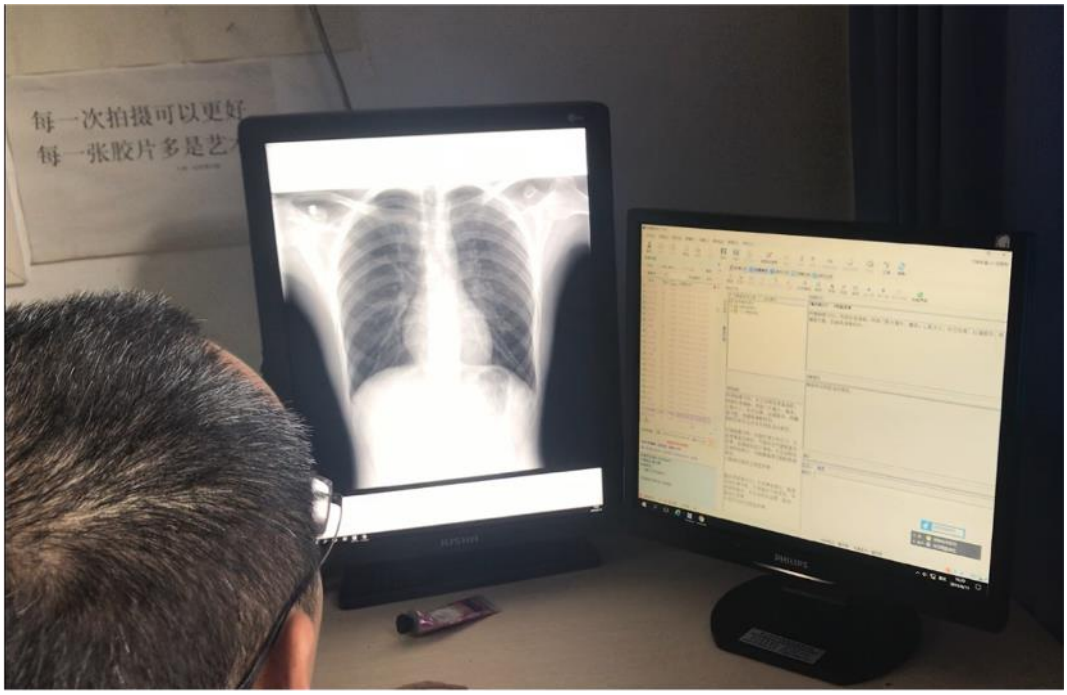
- Bluetooth connection between the laptop and the detector was slow, and sometimes the connection was lost altogether. It was also possible to connect the laptop and the detector via ethernet cable. However, the ethernet cable was too short to suit the project team's needs.
- Battery life without the power bank was too short for the high throughput goal of the project; but the power bank also limited throughput by constantly requiring the generator to be switched on and off.

Watch a video of their screening activities:

https://www.youtube.com/watch?v=TrcQP6GZnxI

Screening university students for TB and other abnormalities in China.

Project dates: 15 August – 27 August 2020
Local Implementing Organization: Tsinghua University Hospital
Country: China
Project setting: University Hospital in Beijing
CAD software: InferRead DR Chest



Implementation and operation

- InferRead DR Chest was used to analyze the CXRs of new university students for TB and other abnormalities, such as tumors and fractures.
- The screening team included two radiologists, two physicians, three to four nurses, and administrative assistants who registered the patients. In total, the project included seven radiologists who rotated reading duties.
- This was the first large-scale CAD screening project in China. In total, more than 8,000 people were screened in eight days, identifying six TB cases.
- All forms of CAD output were used (abnormality scores, heatmap diagram and report). However, the CAD output was used only as reference, and was not in the final report.
- If InferRead DR Chest indicated the presence of TB-related abnormalities, a radiologist would review the CXR and reported symptoms. Based on the radiologist's recommendation, a diagnostic CT scan would be performed on these patients.
- If a disease was confirmed, follow-up care was conducted by the local TB specialization unit under the direction of the Center for Disease Control in Beijing.
- The CXRs were performed with all the requisite radiation protection measures in place.

Field set-up and configuration

Hardware: Three X-ray devices of the same brand (GE) were used. They were connected to three workstations, which were linked to a centralized

server. The InferRead DR Chest was installed on the centralized server to analyze the images.

Internet requirement: InferRead DR was deployed offline.

Integration: with a local PACS (Zhong Lian PACS) and was performed by Infervision.

Data storage: CXRs were stored on the hospital PACS and were not connected to larger data management systems.

Validation was conducted by Infervision using 200 images randomly sampled from the hospital's daily intake of chest X-rays. This validation occurred before InferRead DR Chest was used for screening.

Threshold score selection

The **threshold score** was chosen based on the manufacturer's validation studies. The threshold optimized the sensitivity and specificity of InferRead DR Chest and focused on reducing the number of missed cases.

Key Implementation Considerations

Data privacy

- A **local server** was chosen to ensure patient data remained within the hospital.
- **De-identification** of patient data was performed automatically by the CAD, with only an examination number and time attached to the DICOM.

Training, service, and maintenance

- **Installation** was conducted jointly by Infervision and the IT specialists at the hospital. The X-ray manufacturer was not engaged in the installation.
- **In-person** training was provided by Infervision for groups and, if necessary, on an individual basis. **Online training material** was also available to supplement the in-person training.
- **IT support** was regularly provided by Infervision, and technical problems were quickly resolved.

Highlights

- Radiologists and physicians said that InferRead DR Chest was accurate, easy to use, and integrated well with workflow. It also made report writing faster, reducing their workload.
- Optical character recognition (OCR) software was an add-on feature provided by the CAD supplier. It helped by automatically recognizing patient IDs, enabling users to switch easily between PACS and AI systems.

Challenges

- The cost of the examinations is usually passed on to the patients. This might prove logistically challenging, with license-fee based CAD pricing, rather than pay-per-use structures.
- As with all AI, the possibility of false negative results could result in missed cases.

References

1. World Health Organization. *Global Tuberculosis Report 2020*.; 2020. http://apps.who.int/bookorders. Accessed March 26, 2021.
2. Pande T, Pai M, Khan FA, Denkinger CM. Use of chest radiography in the 22 highest tuberculosis burden countries. *Eur Respir J*. 2015;46(6):1816-1819. doi:10.1183/13993003.01064-2015
3. World Health Organization. *Chest Radiography in Tuberculosis Detection: Summary of Current WHO Recommendations and Guidance on Programmatic Approaches*.; 2016. http://www.who.int/about/licensing/copyright_form. Accessed March 26, 2021.
4. World Health Organization. *WHO Consolidated Guidelines on Tuberculosis*.
5. World Health Organization. *Module 2: Screening WHO Operational Handbook on Tuberculosis Systematic Screening for Tuberculosis Disease*. https://apps.who.int/iris/bitstream/handle/10665/340256/9789240022614-eng.pdf. Accessed March 26, 2021.
6. Meskó B, Görög M. A short guide for medical professionals in the era of artificial intelligence. *npj Digit Med*. 2020;3(1):1-8. doi:10.1038/s41746-020-00333-z
7. Artificial intelligence is changing these 9 industries. https://www.businessinsider.com/sc/artificial-intelligence-companies?r=US&IR=T. Accessed March 26, 2021.
8. How AI is Being Deployed Across Industries. https://www.roboticsbusinessreview.com/ai/infographic-how-ai-is-being-deployed-across-industries/. Accessed March 26, 2021.
9. Chartrand G, Cheng PM, Vorontsov E, et al. Deep learning: A primer for radiologists. *Radiographics*. 2017;37(7):2113-2131. doi:10.1148/rg.2017170077
10. Qin ZZ, Naheyan T, Ruhwald M, et al. A new resource on artificial intelligence powered computer automated detection software products for tuberculosis programmes and implementers. *Tuberculosis*. 2021;127:102049. doi:10.1016/j.tube.2020.102049
11. AI Products for Tuberculosis Healthcare | AI4HLTH. https://www.ai4hlth.org/. Accessed March 26, 2021.
12. Qin ZZ, Sander MS, Rai B, et al. Using artificial intelligence to read chest radiographs for tuberculosis detection: A multi-site evaluation of the diagnostic accuracy of three deep learning systems. *Sci Rep*. 2019;9(1):1-10. doi:10.1038/s41598-019-51503-3
13. Qin ZZ, Ahmed S, Shahnewaz S, et al. (in press). Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms. *Lancet Digit Heal*. 2021.
14. Murphy K, Habib SS, Zaidi SMA, et al. Computer aided detection of tuberculosis on chest radiographs: An evaluation of the CAD4TB v6 system. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-62148-y
15. Rahman MT, Codlin AJ, Rahman MM, et al. An evaluation of automated chest radiography reading software for tuberculosis screening among public- and private-sector patients. *Eur Respir J*. 2017;49(5). doi:10.1183/13993003.02159-2016
16. Nash M, Kadavigere R, Andrade J, et al. Deep learning, computer-aided radiography

reading for tuberculosis: a diagnostic accuracy study from a tertiary hospital in India. *Sci Rep*. 2020;10(1):1-10. doi:10.1038/s41598-019-56589-3

17. Saito T, Rehmsmeier M. The Precision-Recall Plot Is More Informative than the ROC Plot When Evaluating Binary Classifiers on Imbalanced Datasets. 2015. doi:10.1371/journal.pone.0118432

18. *High-Priority Target Product Profiles for New Tuberculosis Diagnostics: Report of a Consensus Meeting*. www.who.int. Accessed April 28, 2021.

19. Philipsen RHHM, Sánchez CI, Maduskar P, et al. Automated chest-radiography as a triage for Xpert testing in resource-constrained settings: A prospective study of diagnostic accuracy and costs. *Sci Rep*. 2015;5(1):12215. doi:10.1038/srep12215

20. Muyoyeta M, Maduskar P, Moyo M, et al. The Sensitivity and Specificity of Using a Computer Aided Diagnosis Program for Automatically Scoring Chest X-Rays of Presumptive TB Patients Compared with Xpert MTB/RIF in Lusaka Zambia. Wilkinson RJ, ed. *PLoS One*. 2014;9(4):e93757. doi:10.1371/journal.pone.0093757

21. FIND. *Digital Chest Radiography and Computer-Aided Detection (CAD) Solutions for Tuberculosis Diagnostics: Technology Landscape Analysis*.; 2021.

22. Esteva A, Robicquet A, Ramsundar B, et al. A guide to deep learning in healthcare. *Nat Med*. 2019;25(1):24-29. doi:10.1038/s41591-018-0316-z

23. Gentle Dive into Math Behind Convolutional Neural Networks | by Piotr Skalski | Towards Data Science. https://towardsdatascience.com/gentle-dive-into-math-behind-convolutional-neural-networks-79a07dd44cf9. Accessed March 26, 2021.

24. Understanding CNN (Convolutional Neural Network) | by Vincent Tatan | Towards Data Science. https://towardsdatascience.com/understanding-cnn-convolutional-neural-network-69fd626ee7d4. Accessed March 26, 2021.

25. Sidey-Gibbons JAM, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction. *BMC Med Res Methodol*. 2019;19(1):64. doi:10.1186/s12874-019-0681-4

Annexes

http://www.stoptb.org/dhthub/practicalguide.asp