Chapter 6

# The evolution of imaging and portable imaging tools to aid tuberculosis diagnosis

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Imaging has a long history as an aid to the diagnosis of TB. In recent years, the pace of technological development in the imaging of TB has been rapid, with the arrival of ultra-portable CXR and point-of-care ultrasound (POCUS) devices, as well as substantial advances made in computer-aided detection (CAD) of CXRs, leading to the WHO's landmark 2021 recommendation of CAD as an alternative to human interpretation of digital CXRs for the screening of TB. However, the evidence is currently limited and of low quality for the use of POCUS as a diagnostic aid for TB. In this chapter, we review the current status of these imaging tools to aid TB diagnosis.

## Introduction

The use of imaging to aid the diagnosis of TB has a long history. Almost as soon as X-rays were discovered in 1895, their potential utility for the identification of PTB was recognised [1].

In 1974, the era of mass radiography for TB screening came to an end when the WHO recommended that "indiscriminate TB case finding by mobile mass radiography should now be abandoned", noting that it was expensive, required highly qualified staff and could not be used alone to establish a diagnosis of TB. Instead, the WHO promoted sputum smear microscopy of symptomatic individuals, and microscopy became a major part of the DOTS strategy [2].

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It was gradually recognised that HIV-associated TB is more likely to be sputum smear negative [3]. This discovery led to a 2007 WHO recommendation for prompt CXR in PLHIV with smear-negative presumptive TB [4]. In addition, the development of molecular tests that are more sensitive, more specific and substantially more expensive than smear microscopy created the need for a screening test to identify patients who should be evaluated with the new molecular tools [5]. Symptom-based screening is a limited tool for this use case, suffering from a high number needed to screen in most populations [6–8]. By contrast, with its high sensitivity and relatively low cost, CXR is an excellent tool for this use case [9], including in PLHIV, although its sensitivity is lower than among HIV-negative people, especially in children [10]. Finally, prevalence surveys show that a substantial proportion of TB cases are asymptomatic but detectable by CXR followed by microbiological testing, a state that has been reclassified as subclinical TB [11] and which is likely to play an important role in TB transmission at the population level [12].

Given the 2015 End TB Strategy's focus on the early detection and treatment of all patients with TB [13, 14], imaging has a vital role to play as a screening tool and to support clinical diagnosis in people who are unable to produce sputum [15, 16]. In recent years, the pace of technological development in the imaging of TB has been rapid, with substantial advances made in artificial intelligence (AI) and computer-aided detection (CAD) of CXRs, and with the arrival on the global market of new portable and ultra-portable CXR and point-of-care ultrasound (POCUS) devices. In this chapter, we review recent developments in CXR and POCUS hardware and interpretation, as well as the evidence and new global policy surrounding their use.

## CXR

In 2007, the WHO noted that "the limitations that exist on the wider use of CXR, such as nonavailability at peripheral health facilities and the difficulty of interpreting results, even by trained physicians, need to be addressed, including through training" [4]. Sixteen years later, these limitations largely remain in place. Although CXR is a relatively inexpensive technology per patient when compared with molecular tests for TB, the upfront investment costs in terms of both hardware and the requirement for skilled technicians and radiology staff to create and interpret the images limit its availability in many low-resource, high-TB-burden settings, especially at the primary-care level [17, 18]. A 2015 survey of national TB programmes in 22 countries found that cost was a major barrier to the rollout of CXR in 68% of countries, with 73% lacking equipment such as vans to enable transportation of CXR machines and 59% lacking qualified readers such as radiologists [19]. A 2021 study of diagnostic availability in 10 low–middle-income countries found that only 61.5% of surveyed hospitals had access to any X-ray equipment [20], with access at the community level, where many patients first seek care, likely to be substantially worse [19, 21, 22]. These access limitations have important consequences, as CXR is currently recommended by the WHO in several different use cases for the prevention and diagnosis of TB (table 1).

Given these recommendations by the WHO, there has been substantial interest in recent developments in both CXR hardware and CXR interpretation software that may help to bridge these access gaps.

### *CXR hardware*

There are two stages to producing a CXR image. First, beams of X-rays produced by a generator are fired through a patient's chest into an image receptor, creating a latent image.

**TABLE 1** Current WHO recommendations for the use of CXR in TB

| WHO consolidated TB guideline module[#] | Recommendations around the use of CXR | Study [ref.] |
|---|---|---|
| **Prevention (2020)** | CXR may be offered to PLHIV on ART, and TPT given to those with no abnormal radiographic findings<br>The absence of any symptoms of TB and the absence of abnormal CXR findings may be used to rule out active TB disease among HIV-negative household contacts aged ⩾5 years and other risk groups before TPT | WHO [23] |
| **Screening (2021)** | Among individuals aged ⩾15 years in populations in which TB screening is recommended, systematic screening for TB disease may be conducted using a symptom screen, CXR or molecular WHO-recommended rapid diagnostic tests, alone or in combination<br>Among individuals aged ⩾15 years in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital CXR for screening for TB disease<br>Among adults and adolescents living with HIV, CXR may be used to screen for TB disease | WHO [9] |
| **Children and adolescents (2022)** | In children with presumptive PTB attending healthcare facilities, integrated treatment decision algorithms (flowcharts allocating evidence-based scores to microbiological, clinical and radiological features) may be used to diagnose PTB | WHO [16] |

[#]: module refers to the five modules currently comprising the WHO consolidated guidelines on TB.

Second, the latent image received by the receptor is processed into a radiographic image [24]. In conventional analogue radiography, the receptor is a piece of X-ray film. Analogue radiography has several limitations: film processing is labour intensive, often requiring a dark room and involving chemicals that can be hazardous to those using them [25, 26], image quality is variable [27], and without an additional digitalisation step, the images cannot be digitally stored or used for automated image reading. Despite the 20th-century history of mobile, mass CXR screening, it is also difficult to implement as a portable technology unattached to health facilities, given the complex image processing requirements [28]. Two newer technologies, computed radiography (CR) and digital radiography (DR), provide improvements over analogue radiography.

In CR, the receptor is a reusable phosphor plate, which is scanned by a digitiser and processed into a digital image [25, 28]. This allows substantially faster throughput than analogue radiography but is still slower than DR, in which the receptor is a digital flat-panel detector, removing the need for the intermediate processing stage [28]. Both CR and DR require computing infrastructure, as well as picture archiving and communication systems [28]. As well as offering speed improvements, DR offers the best image quality and is safer for patients because it requires lower doses of radiation than the other technologies. Nevertheless, the preferred system in low–middle-income countries remains CR, primarily due to the capital investment required to implement fully digital stationary radiography equipment, as described later. Moreover, DR requires an X-ray generator calibrated to the specific detector for optimal use, and these generators are fragile, making their transportation to remote settings challenging. Although analogue generators can be retrofitted with digital detector panels, providing better performance than analogue radiography or CR, their performance is still slightly inferior to fully


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DR [28]. Fully DR became available more than a decade ago as stationary equipment intended for general applications in hospitals and clinics. Equipment costs range from US$43 000 to US $140 000, with CE- or US Food and Drug Administration-approved products generally costing >US$100 000. The equipment requires a stable power supply for the X-ray generator and cannot easily be transported to multiple sites, making it unsuitable for many remote settings. By contrast, a CR digitiser that can be used with an analogue generator costs ∼US$10 000 [28].

More recently, developments in detector technology have allowed the production of so-called portable and ultra-portable X-ray systems, although the nomenclature used to describe them sometimes varies and overlaps. According to technical specifications produced by the WHO and the International Atomic Energy Agency, these systems "are designed to be used mainly, but not exclusively, when the planned diagnostic and/or screening activities are located far from health structures or in any case when multiple outreach interventions are socially or economically convenient and considered an advantage" [29]. Despite their increased portability, these systems must still follow the "as low as reasonably achievable" principle of managing radiation exposure for healthcare workers [30].

Portable systems are lighter and easier to assemble and disassemble than stationary systems. They can be loaded into cars for transportation to healthcare facilities or temporary clinics, including those with intermittent power supplies, or installed inside large vans for community-based screening [28]. Ultra-portable systems (figure 1) are the newest hardware development. They are small enough to fit in a backpack, weigh <20 kg and are fully battery operated, making them ideal for use in hard-to-reach areas lacking a power supply or as part of event-based screening [28]. Portable and ultra-portable systems have similar, or slightly lower, upfront costs compared with stationary equipment, but each increasing level of portability is associated with a reduction in throughput: while stationary equipment can process more than 300 CXRs per day, ultra-portable systems can manage fewer than 100 per day [28].


**FIGURE 1** An ultra-portable digital X-ray system.

A 2021 landscape analysis found eight digital stationary CXR products suitable for TB programmes and 21 portable and ultra-portable products [28], evidence of a growing global market in this product area with multiple competing manufacturers. However, published evidence of their use is limited. A portable system is currently being evaluated by the national TB programme of Peru in a Global Fund-supported project [31]. An early evaluation of an ultra-portable system conducted in Vietnam showed promising results, with no significant difference found in mean AI abnormality scores between radiographs produced using the ultra-portable system and those produced using a stationary system on the same patients, in both a national hospital and a community screening setting [32]. The Stop TB Partnership is currently undertaking a project deploying these systems in "hard-to-reach populations that currently face barriers to accessing services" in seven countries [33], early findings from which are highlighting the need for guidance on radiation protection for staff suitable for these ultra-portable machines to ensure more widespread uptake outside health facilities (Z.Z. Qin, Stop TB Partnership, Geneva, Switzerland; personal communication). Two of the ultra-portable systems are available at negotiated prices through the Stop TB Partnership's Global Drug Facility [34], and the Partnership offers a practical guide to their use for TB screening [35]. The Fujifilm FDR Xair System full kit is available for US$47 000, and the Delft Light full kit is available for US$66 750 *via* the Global Drug Facility. Thus, even ultra-portable X-ray systems are expensive, and this poses a major concern for the wider use of these technologies in low-income countries.

### *CAD of CXR*

Historically, interobserver variation during radiograph interpretation and challenges in finding trained radiologists in low-resource settings have always been major barriers. In 2021, the WHO recommended CAD for the first time as an alternative to human interpretation of digital CXRs for the screening of TB in individuals aged ⩾15 years [9]. Product development in this space has been extremely rapid. In 2017, only one CAD product evaluating CXR findings suggestive of TB was commercially available [6]. A continually updated landscape analysis currently shows 13 TB-specific CAD products on the market [36], most with certifications including CE marking from the European Union [37], and several more in the development or validation stages [38].

These CAD products use AI to detect CXR abnormalities that are associated with TB (figure 2) [39]. Specifically, they use deep neural networks, a machine-learning technique, to train using datasets comprising large numbers of CXR images from patients with and without TB [35]. These training datasets are generally labelled based on other sources of information (*e.g.* labelled as "TB" or "not TB" based on linked results from molecular, culture or other tests performed on the same patients, as well as radiologist readings), allowing the neural network to compare its performance with the so-called ground truth of the labelling in a process known as supervised learning [35]. Producing accurate CAD models requires millions of iterations of this process using CXR image datasets that are as large as possible [35]. Most CAD products can be used with any computed or DR system that produces digital images in the correct DICOM (Digital Imaging and Communications in Medicine) format [28]. Some portable and ultra-portable X-ray systems can be also purchased in bundles that include CAD products [28].

CAD products typically give their CXR interpretation in the form of an abnormality score (*e.g.* between 0 and 1 or 0 and 100), with increasing numbers indicating a higher estimated likelihood of TB [40]. Abnormality scores can be given a threshold by the user to indicate whether the patient requires referral for further TB testing, although many companies provide


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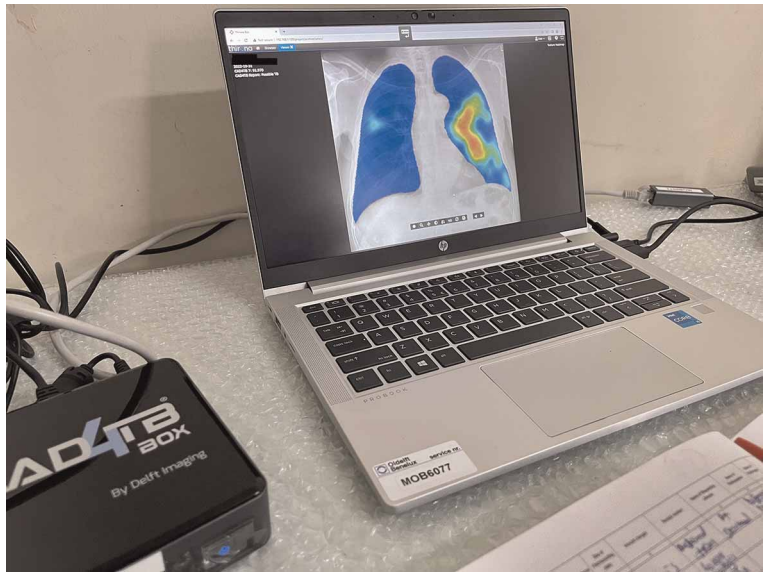


**FIGURE 2** Computer-aided detection of CXR abnormalities in a TB clinic.

pre-set thresholds with their products [41]. Thresholds can be altered in different settings depending on the use case, patient population characteristics and local service capacity for follow-on diagnostic testing [41].

CAD products appear to have at least equivalent accuracy to human readers for the screening of TB. Two systematic reviews from 2019 and 2022 found generally high accuracy for a range of CAD products, although meta-analysed estimates could not be produced due to heterogeneous study designs, methodological limitations, and concerns about the use of overlapping datasets of CXR images for training and testing [42, 43]. In three evaluations conducted on behalf of the WHO to inform their updated 2021 guideline, human radiologists and CAD products were compared directly using libraries of fresh images on which the CAD had not been trained. Both humans and CAD showed variable accuracy across settings and populations, but their sensitivity and specificity estimates overlapped. The WHO therefore concluded that there is little difference between the two, and recommended any CAD products that demonstrate noninferior performance on external validation to those evaluated in their guideline [9]. Subsequent analysis of five CAD products using a large fresh dataset found that all five products significantly outperformed human radiologists in three TB screening centres in Bangladesh [40].

Unlike traditional diagnostic tests, CAD products can be updated rapidly. A 2022 study comparing two of the CAD product versions evaluated by the WHO with their subsequent version updates on fresh image sets found that the newer versions significantly outperformed the older ones [44]. Although this presents obvious advantages as manufacturers can rapidly roll out updated and improved versions to their users globally, it also presents a challenge for programmes using the technology: a given threshold score will not always be associated with the same diagnostic accuracy in different versions of the same product, meaning that software updates may require programmes to adjust threshold scores to maintain the same performance and keep referrals for follow-on testing within local capacity [44]. In response to this challenge,

FIND (the global alliance for diagnostics) has recently developed a validation platform that performs independent analysis of AI-based diagnostic products on diverse datasets. The platform consists of a third-party digital infrastructure for fast and standardised *in silico* assessment of CAD products (in addition to other digital diagnostics) on high-quality clinical, laboratory and digital imaging data collected by FIND in collaboration with partners in multiple countries. These assessments are designed to highlight where performance in specific populations may differ from those on which the products were trained [45].

The potential utility of these CAD products is large as a replacement for human readers in locations that lack such health workers and as an aid to human readers to reduce their workload and highlight abnormal images requiring prioritisation [35, 41], as well as being part of integrated disease screening efforts [46], which could help advance the universal health coverage agenda. However, they have some limitations. First, as neural networks process information in a manner beyond the understanding of users, and the algorithms underlying them are business secrets, a CAD product can be seen as a black box, reaching a decision through a process that is effectively impossible for a user to explain [35, 44]. This opacity means that each software update should be treated as an entirely new product for evaluation as it may have involved significant changes to the neural network that cannot be understood from the outside [36]. Unbiased software evaluations of the latest versions created using datasets from different parts of the world will therefore be vital for both maintaining trust in CAD products and for allowing users to understand the programmatic implications of the updated products [44]. The WHO is currently creating a set of requirements for CAD for TB as part of a prequalification technical specification that will include guidance on the validation method for CAD products [47], and the FIND validation platform mentioned earlier will support this work [45].

Second, CAD products have infrastructure, training and other requirements that may prove challenging. For example, an early evaluation of a CAD product for TB screening in five primary health centres in Peru found that limited internet connectivity, lack of access to radiograph viewers and heavy health worker workloads discouraged use of the product [48]. In addition, these products are currently only recommended by the WHO for the screening of TB, and not as products suitable for the general interpretation of CXR for any indication, a clear disadvantage when compared with human readers. General CXR interpretation is much more technically challenging than the diagnosis of an individual disease, and although CAD has seen expansion into non-TB use cases such as cancer and COVID-19, it does not yet cover all possible use cases [49–51]. Lastly, current CAD products are not validated for use in children, and this is a key evidence gap that must be addressed.

## Ultrasound

Like CXR, ultrasound hardware has developed rapidly in recent years. Modern POCUS devices are inexpensive, safe and highly portable [52]. A 2023 study from the UK found that POCUS devices ranged in price from £2 500 to £6 000, compared with ~£30 000 for a traditional hospital ultrasound device [53]. They can run on battery power and are increasingly used by nonradiologist healthcare staff for a range of indications in hospital and primary-care settings worldwide (figure 3) [54–57]. Given the high hardware cost of CXR and access challenges to CXR in many high-TB-burden settings, utilising POCUS for the screening of TB could substantially widen access to imaging for TB. However, evidence is currently limited and of low quality for the use of POCUS as a diagnostic aid for both PTB and EPTB. AI interpretation of ultrasound images has been attempted for many anatomical regions of the body [58, 59], but has yet to overcome critical issues for use in TB screening and diagnosis, in part due to a lack of appropriate databases of ultrasound images on which to train the AI [60].


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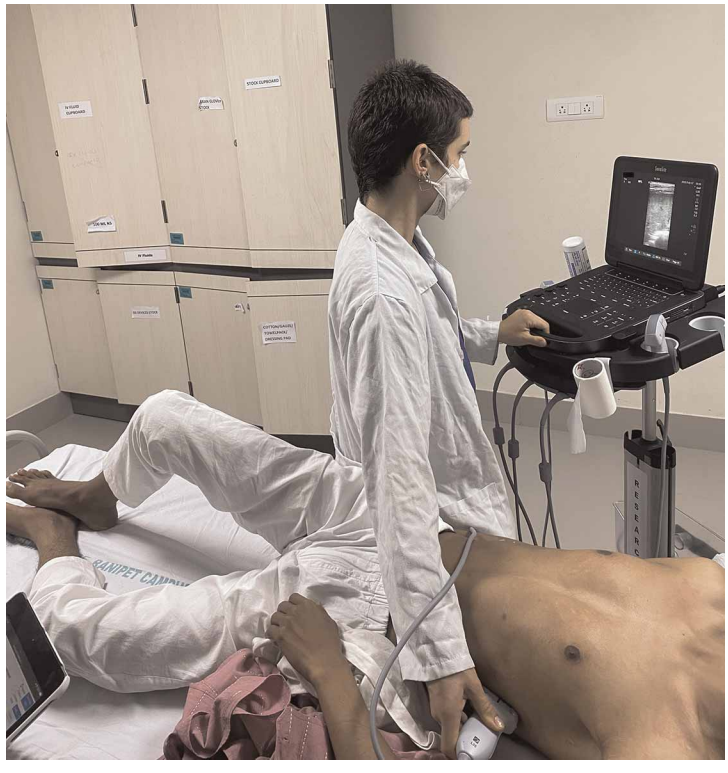

**FIGURE 3** Ultrasound machine in use in a tertiary care centre in India. Image provided by and reproduced with the kind permission of Stefan Weber (Division of Infectious Disease and Tropical Medicine, Department of Infectious Diseases, Heidelberg University Hospital, Heidelberg, Germany).

### *POCUS for EPTB*

Among people who develop TB, EPTB is more common in PLHIV than in those without HIV and is more common in children than in adults [61]. In 2012, a protocol was developed for focused assessment with sonography for HIV-associated TB (FASH), a triaging ultrasound scan comprising six probe positions on the thorax and abdomen that aims to identify signs consistent with EPTB that should prompt further investigation [62]. A 2019 Cochrane Review found that the use of FASH or similar abdominal ultrasound scans had a pooled sensitivity and specificity of 63% and 68%, respectively [63], and can be used in combination with other diagnostic strategies for EPTB, although the data were limited and of low certainty [63]. A randomised controlled trial of the use of an extended version of FASH, known as eFASH, in Tanzania found that eFASH did not increase the proportion of patients who were correctly managed at 6 months (the study's primary outcome), but it did increase the proportion of patients diagnosed with definite TB [64].

### *POCUS for PTB*

For the diagnosis of adult pneumonia, lung ultrasound has at least equivalent sensitivity and specificity to CXR [65]. A finding that POCUS has similar diagnostic accuracy to CXR for PTB would be an important development. However, the current evidence base is limited and of poor quality. A 2021 systematic review found few studies and could not produce pooled

accuracy estimates due to methodological flaws and heterogeneity in study reference standards [66]. Variability in sensitivity of POCUS signs for PTB found in the systematic review may imply operator dependence, a weakness that has been identified by other authors [67]. Additionally, image acquisition and image analysis protocols have not been clearly defined for POCUS for PTB [66], unlike the FASH protocol for EPTB [62].

In summary, additional optimisation and evaluation are needed to assess the potential use of POCUS for TB, especially among children and other populations where conventional tests are likely to underperform.

## Conclusion

The use of imaging to aid the diagnosis of TB has a long and varied history. CXR is currently recommended by the WHO in several different use cases for the prevention and diagnosis of TB, but CXR access is limited in many low-resource, high-TB-burden settings. Recent developments in portable and ultra-portable digital CXR systems have the potential to substantially widen access to imaging for TB, but the high cost of hardware is a concern for scale-up in low-resource settings. The development of more affordable digital X-ray systems could greatly help, as X-rays are needed for diverse conditions at the primary-care level. In 2021, CAD was recommended by the WHO as an alternative to human interpretation of digital CXRs and also has the potential to widen access to imaging for TB. However, the neural networks underlying these CAD products reach decisions through opaque processes, and the rapid speed of product development creates programmatic challenges for their use. Lack of evidence on CAD for use in children is a key evidence gap that must be addressed. The recent introduction of a validation platform that performs independent analysis of AI-based diagnostic products will strengthen global systems for the evaluation of CAD products, as will the upcoming WHO prequalification technical specification for these products. POCUS is much less expensive than CXR but is not as validated as CXR for TB. POCUS has moderate diagnostic accuracy for EPTB, while the current evidence base for POCUS for PTB is limited and of poor quality. Additional optimisation and evaluation are needed for POCUS as a screening test for TB.

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