Digital Radiology Solutions for TB Diagnostics in Low- and Middle-income Countries
Contents
Executive Summary .............................................................................................................................................. 5
    Background .................................................................................................................................................. 5
    Rationale ................................................................................................................................................ 5
    Findings .................................................................................................................................................. 6
    Conclusions .......................................................................................................................................... 6
Section 1: Introduction .................................................................................................................................... 6
    Rationale ................................................................................................................................................ 6
    Methodology and conflicts of interest ........................................................................................................ 6
    CXR in TB diagnostics ............................................................................................................................... 7
Section 2: Overview: X-ray Technology for CXR ........................................................................................... 8
    Conventional imaging ................................................................................................................................. 8
    Computed radiography .............................................................................................................................. 8
    Digital radiography ................................................................................................................................ 10
Section 3: Ideal CXR Solution for TB Diagnostics in LMICs ......................................................................... 12
    What kind of x-ray machine will serve the purpose? .................................................................................... 12
    Will a small mobile x-ray machine serve the purpose? ............................................................................. 14
Section 4: Detector Based Digital X-ray Imaging: Technology and Market Landscape ......................... 15
    Leading manufacturers and products: digital detector technology .......................................................... 17
    X-ray detectors market, by application ...................................................................................................... 17
    Leading manufacturers in detector technology .......................................................................................... 17
    Cost of detectors .................................................................................................................................. 18
    Research and development in low-cost detector technology .................................................................. 21
Section 5: X-ray Equipment Market Landscape .......................................................................................... 21
    Easy DR Digital X-ray (Delft Imaging Systems) ....................................................................................... 23
    Xplorerer 1500 (Imaging Dynamics Company) ......................................................................................... 23
    DCElite (Del Medical, Inc) ....................................................................................................................... 24
    EcoView9 Chest Exam (Ecoray) ................................................................................................................ 25
    Chiro System (CONTROL-X MEDICAL) .................................................................................................... 25
ddRElement (Swissray) ................................................................. 26
Research and development in low-cost x-ray technology ......................................................... 27
Section 6: Readout Solutions /CAD Market Landscape ............................................................. 28
   CAD4TB .................................................................................. 29
   DigiportXCAD ........................................................................ 30
   ClearRead ............................................................................. 30
Section 7: Discussion .................................................................................. 31
Section 8: Conclusion .................................................................................. 32
References ......................................................................................... 33
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>Acid fast bacilli</td>
</tr>
<tr>
<td>a-Si</td>
<td>Amorphous silicon</td>
</tr>
<tr>
<td>ATT</td>
<td>Anti-tuberculosis treatment</td>
</tr>
<tr>
<td>CAD</td>
<td>Computer-aided detection</td>
</tr>
<tr>
<td>CAGR</td>
<td>Continuous annual growth rate</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge coupled device</td>
</tr>
<tr>
<td>CR</td>
<td>Computed radiography</td>
</tr>
<tr>
<td>CsI</td>
<td>Cesium iodide</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DIAG</td>
<td>Diagnostic imaging group</td>
</tr>
<tr>
<td>DQE</td>
<td>Detective quantum efficiency</td>
</tr>
<tr>
<td>DR</td>
<td>Digital radiography</td>
</tr>
<tr>
<td>FPD</td>
<td>Flat panel detector</td>
</tr>
<tr>
<td>Gadox</td>
<td>Gadolinium oxysulphide</td>
</tr>
<tr>
<td>GOS</td>
<td>Gadolinium oxysulphide</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low- and middle-income country</td>
</tr>
<tr>
<td>MTF</td>
<td>Modulation transfer function</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>PACS</td>
<td>Picture archival communication system</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>PTB</td>
<td>Primary tuberculosis</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TFT</td>
<td>Thin-film transistors</td>
</tr>
<tr>
<td>V</td>
<td>Volt</td>
</tr>
</tbody>
</table>
Executive Summary

Background
Tuberculosis (TB) is a contagious bacterial disease caused by the acid-fast bacilli (AFB) *Mycobacterium tuberculosis*, which primarily affects the lungs.\(^1\) Although there have been remarkable achievements in reducing deaths from TB (about 7 million deaths per year when Robert Koch discovered the TB bacterium in 1824), it still accounts for nearly 1.5 million deaths per year.\(^1,2\)

Chest x-rays (CXR) have played a historic role in TB diagnostics, especially in the case of pulmonary TB (PTB), which is one of the most common presentations of all forms of TB. Although chest x-rays are not the gold standard for confirming a diagnosis of TB, they do offer a high sensitivity for detecting PTB-related abnormalities in lungs (opacities, scars, pleural effusion, etc.). Additionally, because chest x-rays can enable rapid examination with onsite interpretation, chest radiography has been recognized as a powerful screening test for TB, especially in low- and middle-income countries (LMICs) with higher burdens of the disease.\(^3\)

A number of technical challenges involved in the production of interpretable radiographs (accurate positioning, reproducibility in subsequent images, maintaining uniform optical density of anatomic structures irrespective of variations in body size/shapes, etc.). Furthermore, lower specificity and greater extent of variability in diagnostic results is due to the variation in skills/experience of image interpreters. These issues present a substantial challenge in establishing chest radiography as an integral component of the TB diagnostic algorithm.

Advancements in digital chest radiography have revolutionized the process of image acquisition whilst maintaining high diagnostic quality as well as consistency of images produced. Developments in x-ray detector technology, digital image storage and computer-aided detection (CAD) are added features that substantially cut down the cost of producing chest radiographs by eliminating the need for film-based radiography/processing chemistry. An additional benefit of digital radiography is a reduction in the number of specialized staff needed throughout the image-taking and interpretation process, particularly as specialized staff is often scarce.

Rationale
This report aims to inform the landscape of digital chest radiography for TB diagnosis in LMICs by using a market and literature analysis.
Findings
There is a range of equipment available for image (CXR) acquisition. However, only one dedicated CAD is currently available with promising results for TB screening. Available dedicated digital CXR systems based on detector technology and CAD solutions have the potential to simplify TB screening, but high cost remains a limiting factor for implementation at a population level. The basic design of x-ray systems is similar for most manufacturers, whereas the detector technology differs the most due to the complexity and costs involved in producing compact, light and high-quality detectors.

Conclusions
Despite the advancements in medical imaging, the benefits of digital radiologic technology remain grossly underutilized for TB diagnostics, especially in the context of LMICs. The development of low-cost detector technology together with a robust and simplified x-ray machine is paramount to bringing down the expense of dedicated CXR systems in LMICs. Additionally, it is important to demonstrate to CAD developers that a market for dedicated CAD solutions for TB exists in order to incentivize a competitive drive to increase involvement.

Section 1: Introduction
Rationale
This report aims to inform the landscape of digital chest radiography for TB diagnosis in LMICs by:

- performing a market analysis of available digital radiology solutions (together with CAD);
- exploring market dynamics;
- undertaking a detailed literature review;
- consulting with radiology equipment manufacturers, CAD developers and researchers;
- outlining the progress of radiology and computer science, particularly in relation to the advantages of digital imaging that can be utilized for TB diagnostics in TB high-burden countries;
- highlighting the current ongoing development of digital radiography and how innovations may affect the market of radiology equipment manufacturing and CAD solutions for TB diagnostics; and
- indicating which current solutions have the most potential for TB screening in LMICs.

Methodology and conflicts of interest
This report has been prepared by Yogesh Jha with support from Claudia Denkinger, Head of Tuberculosis Research Programme at FIND, Geneva, Switzerland. Editorial support was provided by Jonathan Mazal, Regional Director of the Americas for the International Society for Radiographers and Radiologic
Technologists (ISRRT). The resources supporting this report have been selected after extensive review of available literature, reports and product brochures and after contacting radiology manufacturers and CAD developers, investigating corporate websites, visiting technical exhibitions and consulting with research scientists working in the field. Yogesh Jha does not have commercial links or receive incentives from any equipment or technology manufacturer and works as an independent consultant for FIND. The information included in the report is current as of March 2015.

CXR in TB diagnostics
CXR play a crucial role in screening of chest and lung abnormalities that may be indicative of current or previous TB infections. However, a CXR cannot confirm a TB diagnosis on its own, mainly because of its limited specificity. That being said, CXRs have high sensitivity (74% to 90% for PTB-related abnormalities and up to 97% if any abnormality is under consideration). This high sensitivity makes this imaging modality one of the principal investigational tools for TB screening at a population level.4-8

The CXR is one of the most commonly requested x-ray examinations. CXR is important in the TB diagnostic algorithm across several high-burden countries. Despite its low specificity, CXR is often used as the only tool prior to initiating anti-tuberculosis treatments (ATT).

Furthermore, CXRs have been used for TB prevalence surveys of lung abnormalities in several countries such as Japan, the Philippines and the Republic of Korea.5 Most national surveys carried out during the past century have used indirect chest X-ray, that is, mass miniature radiography. In recent years, the use of digital x-ray imaging has rapidly replaced conventional film-based radiography.5

There are several challenges associated with use of CXR for TB diagnostics which are primarily due to the need to capture the wide attenuation differences between the lungs and the mediastinum, as well as visualize small contrast differences and fine structural details.3 Lack of consistency in the reporting of images and higher levels of inter/intra-reader variability due to the level of knowledge, training, working conditions and experience of the observer are of serious concern.9-12
Section 2: Overview: X-ray Technology for CXR

Production of CXR images and interpretation for diagnosis are two separate processes involved in TB diagnostics. For the purpose of this report, the technology landscape for each component is discussed separately.

Currently there are three types of technologies in use to produce CXRs:

Conventional imaging
This is the traditional method that is often referred to as film-based radiography and still widely practiced in most of the LMICs with a high burden of TB, especially in peripheral health care facilities. The dependency on x-ray films (made of expensive silver halide crystals), the need for processing chemistry, the use of a dark room, the need for human resources, as well as the difficulty to maintain quality assurance parameters are all factors that limit the wide-scale use of this method for fast and effective TB screening at the population level.

Figure 1: X-ray film and dark room processing (Image source: http://store.xrayvisions.net/Fuji-Super-RX-U-p/fujirx-u.htm, https://themzungudiaries.wordpress.com/2010/08/31/shots-from-arua-hospital)

Computed radiography
Computed radiography (CR) systems are based on storage phosphor technology that has consistently evolved over the past 30 years. This technology eliminates the need for dark-room based processing chemistry, since reusable phosphor plates are used as image receptors (substitute for x-ray film and cassette as used for conventional radiography) and are scanned by laser imagers to convert the stored information into digital images. In the post-image capture phase, the image receptor will need to be scanned by a processing unit and then erased prior to the next exposure. Conventional x-ray equipment
can still be used as an x-ray source, but the CR reader (digitizer with laser scanner) is the primary image processing component of the updated system. For this characteristic, the described set-up is often referred to as semi-digital technology. All the benefits of digital imaging (i.e. excellent image parameters, archiving, sharing and storage) can be harnessed by this combination of conventional x-ray source and digital image processing system.

A functional x-ray unit with CR system requires additional bulky equipment to be installed along with the x-ray machine. It also requires multiple phosphor plates depending upon the frequency of examination and demands greater investment in terms of infrastructure and operational training. The image quality is also susceptible to artefacts requiring periodic cleaning of the phosphor plates and eventual replacement after the shelf life has expired (recommended by manufacturer).

Figure 2: A CR scanner with phosphor plates for image receptors (Image source: http://www.carestream.com/products/radiography/computed-radiography/directview-cr-systems.html)
Digital radiography
Detector-based digital radiography is the latest development in x-ray technology which uses different types of solid-state detectors (flat panel detectors, charge coupled devices) as image receptors and an x-ray source for producing high-quality radiographs. The detectors are compact, lightweight and come in various sizes including portable versions. The advancements in detector technology have been the hallmark of digital radiography systems, increasing dose efficiency, image quality, ease of equipment handling and, ultimately, image throughput.³ It is often considered a complete digital solution for radiography, as it completely eliminates the need for replacing and processing image receptors, unlike film-based or phosphor-based radiography.

Digital flat panel x-ray detectors dramatically reduce the cost per x-ray image produced, as well as the processing time per image, allowing for potentially instant interpretation for an expedited diagnosis. However, considerable initial investment is associated with installation of such units due to the expensive detector technology. Nevertheless, the long-term cost-benefits and the reduced dependency on highly skilled operators definitely favour the initial investment in DR technology for the purpose of TB diagnostics.⁵
Figure 4: Digital Radiography System *(Image source: TOSHIBA Medical Systems)*

Figure 5: Schematic representation of Evolution of x-ray technology *(Image source: http://www.telesystems.co.jp/en/dental/qr/)*
Section 3: Ideal CXR Solution for TB Diagnostics in LMICs

To scale up the use of CXR in TB diagnostics, the entire process of image acquisition has to be simplified without compromising the diagnostic qualities of the image. Application of a proven CAD as a readout solution is also equally important to eliminate the requirement of interpretation of images by an experienced reader (radiologist/chest physician/radiographer). Such a solution is likely to be beneficial for wide-scale application of CXR for larger populations in limited time frames such as with TB prevalence studies. In the context of LMICs, there needs to be a comprehensive “turn-key” system that will include a simple, robust x-ray machine (based on DR technology) capable of producing high-quality digital CXR images and a trusted CAD software as readout solution.

What kind of x-ray machine will serve the purpose?
Any x-ray machine is capable of performing chest radiography. However, analogue images cannot be used with CAD solutions, so the output image must be in digital format.

As mentioned previously, there are two types of technology options available for producing digital x-ray images: CR & DR. CR technology can produce digital images with conventional x-ray equipment, whereas DR systems usually have built-in detector units. Alternatively, any conventional x-ray machine...
(mobile or fixed) can be transformed into DR equipment by adding retrofitted versions of a digital detector. This transformation is gaining popularity in LMICs, but mostly at large hospital settings. This is proving to be an alternative to expensive full DR (sometimes referred to as born DR) systems and carries a relatively reasonable cost.

Technically, any complete basic or DR x-ray machine (even a conventional option + CR or retrofit DR technology) can be selected to produce digital CXR images. There are hundreds of potential system options, but it should be noted that enhancement of conventional machines with CR or retrofit DR versions adds some complication to implementation such as potential mechanical failures, as well as additional space, and skilled human resource requirements. It is beyond the scope of this report to discuss designs of all suitable x-ray systems for chest radiography in LMICs.

For wide scale application of CXR for TB diagnostics in resource constrained settings, the use of complete DR systems is justified on the grounds of simplicity in design, user friendliness, efficiency, reduced susceptibility to mechanical failure and consistency in producing high quality images. The chart below demonstrates the different types of x-ray equipment that can be used for TB diagnosis.

**Figure 6:** Types of x-ray equipment/technology recommended for CXR for TB application in LMICs (Red = not recommended, yellow = can be used but not really recommended, light green = recommended, dark green = strongly recommended)
DR systems are the latest innovation in terms of design and performance of x-ray systems. For this reason they are also costly. Most manufacturers make versatile x-ray machines based on DR technology that can be used for multipurpose radiography. Simplified DR systems designed specifically for chest radiography are not a priority of equipment manufacturers because of thin profit margins due to market demand being based in LMICs with high TB burdens. *For the scope of this report, we tried to short-list simplified designs of DR technology-based x-ray machines that also meet most of the desirable criteria for dedicated CXR application in LMICs* (See Section 5).

Ideal equipment must satisfy the following criteria:

- Produce excellent digital CXR images (using detector technology);
- Robust in design and require minimal maintenance;
- Allow for 4-5 hours of uninterrupted work in situations of unreliable or unavailable electrical supply;
- Resistant to high temperature, humidity and dust;
- User-friendly for operators with limited skills;
- Small in size to allow for mobile installations, such as in a truck or van; and
- Compliant with applicable international standards and regulatory directives.

To find such a unique product is a challenge because of the likely need for collaboration amongst multiple vendors for design and production. *The detector component is the most expensive component of the entire system and most manufacturers outsource this component from leading detector manufacturers.* Hence, the market landscape for detector technology has been individually analysed within this report with the aim of finding a cost-effective digital detector for CXR application in LMICs (See Section 4).

**Will a small mobile x-ray machine serve the purpose?**

There are several models of small and compact mobile x-ray machines on the market. Some of them (like MinXray, [http://www.minxray.com/medical_mobile_imaging_providers.html](http://www.minxray.com/medical_mobile_imaging_providers.html)) have been widely used for the purpose of screening chest radiographs for larger population. They are very compact and can easily be carried in a van. However, experts with considerable experience in radiography, especially in LMICs, argue that such machines are not the ideal solution for CXR for TB diagnostics on wide-scale application.

This type of machine does not have chest stand as it is basically designed for geriatric care at home (where CXRs are mostly taken in supine or recumbent positions) or for mobile radiography inside intensive care units and wards to access fractures and locate tube or catheter positions.
To run CAD for interpretation, CXRs must be taken in perfect positions (standard erect PA). It has been argued that a chest stand can be added from external source, but that combination is problematic. Installation of a stand on site that maintains adequate distance from subject to x-ray source can be problematic. Based on these grounds, small, lightweight mobile x-ray machines do not meet the selection criteria for an ideal machine for CXR for TB application.

The other point is that mobility is not the only ultimate parameter for selection of equipment for CXR for TB application. The ideal equipment is compact, robust, fixed in design (with integrated chest stand) but also with capability for mobile installation, for example, in trucks (see the models discussed in Section 5). A general mobile x-ray machine will have issues with reproducibility of quality CXRs in terms of positioning faults, which may lead to several false-positive diagnoses when run on automated readout solutions.

Similarly, **CAD solutions are provided by specialized CAD developers. It would be helpful if x-ray manufacturers could provide recommendations as to the most appropriate CAD for TB for use with the imaging produced by their own x-ray systems. Unfortunately, such recommendations rarely occur.** The market landscape of CAD solutions for TB has also been analysed within this report. However, the findings were limited (see Section 6).

**Section 4: Detector Based Digital X-ray Imaging: Technology and Market Landscape**

Currently, there are two types of detectors available in the market based on the process of conversion of x-rays to charge.\(^\text{13}\) **Indirect conversion systems or opto-direct systems use a scintillator** (e.g. cesium iodide (CsI) or gadolinium oxysulphide (GOS or Gadox)) layered on top of an array with light-sensitive photodiodes with thin-film transistors (TFTs). The scintillator converts radiation into light that is detected by the photodiode/TFT array. Crystalline scintillators (e.g., CsI) guide the scintillation light through crystalline needles. CsI-photodiode/TFT systems are widely used for chest radiography and provide better direct quantum efficiency (DQE) than standard CR or Gadox-TFT systems.\(^\text{14,15}\)

**Direct conversion systems or electro-direct systems** use a photoconducting layer (amorphous selenium, a-Se), in which the absorbed x-ray energy is directly converted into a charge on top of a TFT array. These types of detectors absorb slightly less x-ray energy (reduced DQE) for vascular or interstitial structures or infiltrate in the lung represented by frequencies below four cycles/mm (factor of 2 compared to CsI-
photodiode/TFT), which makes them slightly less suitable for chest radiography\textsuperscript{15,16} (when compared to indirect conversion system detectors). That being said, the images produced are superior to digital images produced by CR technologies. Detectors based on this technology are slightly cheaper as well, making them applicable to CXR with CAD for TB diagnosis in LMICs.

The performance of such flat panel detectors (FPDs) are determined by a number of parameters such as spatial resolution, edge spread function, line spread function, modulation transfer function (MTF), noise power spectrum and detective quantum efficiency (DQE).\textsuperscript{13} There are other broad parameters, including communication interface, environmental parameters, mechanical parameters and power requirements to be taken into consideration before making context specific selections.

\textbf{Figure 7}: Schematic representation of direct and indirect x-ray detectors

\textbf{Figure 8}: PaxScan 4336R Flat Panel Detector from Varian Medical Systems
Leading manufacturers and products: digital detector technology
North America dominates the x-ray detectors market, with the U.S. accounting for a major market share. However, Asia is expected to grow at the highest continuous annual growth rate (CAGR) over the upcoming years. Emerging economies such as India, China and Brazil present an array of opportunities for this market. The x-ray detectors market size, in terms of value, is expected to reach US$ 2.5 billion by 2019 from US$ 2 billion in 2014, at an annual growth rate of 4.9%.

X-ray detectors market, by application
- Medical applications:
  - Static imaging
    - General radiography
    - Mammography
  - Dynamic imaging
    - Surgical imaging
    - General fluoroscopy
    - Cardiovascular imaging
- Dental applications
- Security applications
- Industrial applications
- Veterinary applications

There are several manufacturers in the digital detector technology market. Some of the manufacturers sell complete DR solutions (detector + x-ray source) whereas others sell detector components externally, the latter being relatively less expensive.

Leading manufacturers in detector technology
- Agfa (Belgium)
- Atlaim (Korea)
- Canon, Inc. (U.S.)
- DRTech (Korea)
- Fujifilm Medical Systems (Japan)
- General Electric (U.S.)
- Hologic (U.S.)
- iRay (China)
- Konica Minolta, Inc. (Japan)
- PerkinElmer (U.S.)
- Rayence (Korea)
- Samsung (Korea)
- Teledyne DALSA (Canada)
- Thales (France)
- Toshiba (Japan)
- Trixell (France)
- Varian Medical Systems (U.S.)
- Vieworks (Korea)
- YXLON (Germany)
There are a range of products based on detector types (indirect capture FPDs/direct capture FPDs), panel size (large area/small area), application (general radiography/mammography/dynamic imaging) as well as a variety of other factors.

Target products for the purposes of this report are general radiography detectors with large surface areas. Both indirect as well as direct FPDs can be used for the purpose of chest radiography. None of the manufacturers develop detectors specifically dedicated to chest radiography but all general radiography detectors can be used for CXR application. The detectors developed are mostly multipurpose with a large active surface area.

Detail specifications of detectors by these manufacturers slightly vary among parameters:
- Detector technology (direct vs. indirect);
- Technical specifications (active area, pixel array, pixel pitch, limiting resolution, MTF, DQE);
- Communication interface (image acquisition time, exposure control, wireless option);
- Environmental condition (operating and storage temperature, humidity);
- Mechanical (dimension, weight, housing material);
- Power (power dissipation, power supply, frequency, battery backup option); and
- Regulatory requirements

Cost of detectors
Cost of detectors depends upon a number of factors, such as whether the system is fitted with a born digital machine (complete DR), comes with retrofit version (docked with analogue equipment to convert into DR) or is purchased independent of the other components. It is less likely that people will go for isolated detectors (unless for replacement purposes). Based on the technology, indirect capture FPDs are more expensive and more recent than direct capture FPDs. For the purpose of general chest radiography, both types can be used.

Major vendors like GE and Varian sell detectors in combination with their own x-ray equipment and they are very costly from the perspective of LMICs (average price for such complete DR machines is US$ 180,000). The price attributable to the detector alone can be as high as US$ 60,000-70,000).

The medium-tier manufacturers like Perkin-Elmer, Toshiba, Canon, Teledyne DALSA and Rayence sell detectors to other vendors. The buyers are usually medium-scale x-ray equipment manufacturers (e.g. Delft Imaging uses Canon detectors). A good quality DR machine for CXR application in LMICs fitted
with such a detector falls within the price range of US$ 100,000-125,000). The information on the isolated expense for the detector component from these manufacturers has proven to be a challenge to obtain, but it is estimated within the range of US$ 40,000-60,000) based on verbal consultation with experts and industry manufacturers. Features such as the size of detector, a wireless option and extended battery life are also contributors to variable prices.

For the purpose of chest radiography, the recommended detector size is 14”×17” (inches), which is generally the largest available size from most manufacturers. In terms of technical features suitable for LMICs, CXR application does not demand high-tech detector features, as this is usually a requirement for dynamic detectors. In addition to robust design, a pixel pitch between 100 to 168 µm, image readout time of 2-6 seconds and a battery life of at least four hours or up to 120 exposures are sufficient to satisfy selection criteria. Almost all general radiography purpose detectors meet these requirements, though slight variability between battery life and robustness in design can be expected. As a result, cost remains the major decisive factor in terms of selection of detector or equipment combination for wide-scale application of CXR in LMICs for TB diagnostics.

The table below shows the technical specifications of some of the detectors from major manufacturers.

**Table 1: Detector specifications from major manufacturers**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Brief specifications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGFA</td>
<td>DX-D Retrofit DX-D 10, DX-D 20 DX-D 30C, DX-D 35C</td>
<td>Amorphous silicon (a-Si) technology, CsI conversion screen, pixel pitch 125 µm, wireless option, extended battery life</td>
<td>Suitable for chest radiography</td>
</tr>
<tr>
<td>Canon</td>
<td>CXDI (701C, 70C, 801C, 80C, 501C, 501G, 401C, 401G, 50RF, 55C, 55G)</td>
<td>FPD technology, compact &amp; wireless options, powerful sensors, pixel pitch 125 µm, less recharge time, readout time 1-2 seconds after exposure, DICOM compatible</td>
<td>Suitable for chest radiography. Canon detectors are being used by Delft Imaging, a pioneer in developing dedicated CXR equipment.</td>
</tr>
<tr>
<td>VARIAN</td>
<td>FDX3543RPW FDX4343RPW FDX3543RP FDX4343R</td>
<td>QADCEL technology-based detectors TFT array + photodiode (a-Si) Pixel pitch 140 to 143 µm Image output time 3-4 seconds</td>
<td>All suitable for chest radiography</td>
</tr>
<tr>
<td>TRiXELL</td>
<td>Pixium 4343 RC / 4343RG Pixium Portable 3543pR</td>
<td>Available in different sizes (41x43 or 43x43) and with different scintillator in CsI and Gadox light, wireless mode</td>
<td>Developer of world's first wireless digital detectors for</td>
</tr>
<tr>
<td>Company</td>
<td>Model</td>
<td>Description</td>
<td>Additional Features</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>PerkinElmer</td>
<td>XRpad 4336, XRpad 4343F</td>
<td>Flat panel detector, produced by PerkinElmer, Uses a-Si technology, 100µm pixel (suited to chest work), Very high resolution images, Image output time 3 seconds.</td>
<td>XRpad 4336 works off rechargeable Li-ion batteries.</td>
</tr>
<tr>
<td>Toshiba</td>
<td>FDX4343R, FDX3543RPW, FDX3543RP</td>
<td>Cesium iodide (CsI) with a-Si, a-Si photodiode, Pixel pitch 140 to 143 µm, High resolution, low noise, Ethernet and wireless options.</td>
<td>Suitable for general radiography and chest.</td>
</tr>
<tr>
<td>Samsung</td>
<td>Retrofit GR40CW (S4335-W, S4335-WV)</td>
<td>CsI direct deposition a-Si TFT, Gadox a-Si TFT, Image output time 3-3.5 seconds.</td>
<td>Suitable for use with any x-ray source.</td>
</tr>
<tr>
<td>Rayence</td>
<td>1417WGB, 1417WCC/WGC, 1417WCA/WGA, 1417PCA/PGA, 1717SCC/SGC</td>
<td>Scintillator Gd2O2S: Tb, CsI: Tl / Gd2O2S: Tb, Pixel pitch 127 µm.</td>
<td>Suitable for general radiography including chest.</td>
</tr>
<tr>
<td>iRay</td>
<td>Venu Series – Tether Detectors, Mars Series – Wireless Detectors</td>
<td>a-Si GOS/CsI, a-Si DRZ PLUS / CSI, Image output time 3-5 seconds, Pixel pitch 139 to 150 µm.</td>
<td>Multi-modality sharing, charging and backup, suitable for general radiography.</td>
</tr>
<tr>
<td>ATLAIM</td>
<td>ATAL 9</td>
<td>a-Si TFT array FPD, Capture cycle time 2-5 seconds, 10 hours of battery life.</td>
<td>Lightweight, portable, good for general radiography.</td>
</tr>
<tr>
<td>DRTech</td>
<td>FLAATZ 600 (portable), FLAATZ 601, 760, 560, 750E, 500, 330N</td>
<td>TFT – Amorphous selenium (direct conversion), pixel pitch 139 – 168 µm, readout time up to 6 seconds, wireless option available.</td>
<td>Suitable for general radiography.</td>
</tr>
<tr>
<td>CARERAY</td>
<td>Careview 1800R, Careview 1500L</td>
<td>CSI direct deposit, Pixel pitch 154 µm, Image output time 2 to 3 sec.</td>
<td>Suitable for chest radiography.</td>
</tr>
<tr>
<td>APEX</td>
<td>FLAATZ 750E, FLAATZ 560, APEX 4343R, APEX3543RP</td>
<td>Fixed and tethered CsI, Pixel pitch 143 µm.</td>
<td>Suitable for general radiography including chest.</td>
</tr>
<tr>
<td>THALES</td>
<td>Piximum Portable 3543 EZ</td>
<td>CsI coupled to TFT matrix a-Si technology, Pixel pitch 148 µm, High-resolution image display &lt;10 seconds, preview in 3 seconds, Battery backup up to 8 hours.</td>
<td>Only 2.8 kg, lightest FPD available, ideal for general radiography including chest.</td>
</tr>
</tbody>
</table>
Research and development in low-cost detector technology

Current models of digital x-ray detector technology are able to answer the needs of TB diagnostics by producing high quality CXR images. However, the cost associated with available detector technology is the major obstacle in widespread implementation within LMICs for TB diagnostic purposes.

There is ongoing research and development to produce low-cost x-ray detectors specifically for lung imaging for TB. For instance, the research team lead by Professor Karim S. Karim, a faculty member in electrical and computer engineering at the University of Waterloo (Canada), is working to develop digital x-ray systems with a smaller-than-average x-ray detector size.  

The proposed innovation in detector design is to use two smaller flat panel detectors for separate lung imaging instead of using the conventional 17-inch square flat panel. After recognizing that a smaller x-ray detector is not sufficient in size to x-ray the average adult’s entire chest, a medical study was undertaken by the University of Waterloo in collaboration with Aga Khan University Hospital (Karachi, Pakistan) to investigate the impact of diagnostic accuracy when using two single-lung images rather than a full chest x-ray. Preliminary results of the study were promising, with findings showing a sensitivity and specificity in favour of the proposed design.  

Section 5: X-ray Equipment Market Landscape

Given that CXRs are one of the most common examinations prescribed worldwide, all x-ray machines are capable of performing them. There is a range of complete DR equipment (x-ray source or camera + detector with bucky system) from various manufacturers, but few of them are actually dedicated to chest radiography only. The big brands in radiology industry (Siemens, General Electric, Philips, Shimadzu and Toshiba) generally focus on multipurpose x-ray equipment that is also capable of chest radiography. This usually complicates the design by requiring greater installation space and adds to the overall cost (not suitable for use in LMICs).

There are also a number of options available from mobile x-ray system manufacturers, but the limitations with such x-ray systems is an absence of dedicated chest stands since most units are designed for use in hospital wards or intensive care units and non-ambulatory patient populations. Some of the medium-scale manufacturers do offer complete dedicated chest x-ray units (x-ray machine with detector component) that are simpler in design and robust enough to be installed in peripheral health care facilities in LMICs.
Table 2: Equipment specification from selected complete DR machines for CXR application in LMICs

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Design</th>
<th>Detector type and specification</th>
<th>Power options</th>
<th>Image readout time and other salient features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy DR Digital x-ray Delf Imaging System, Netherlands</td>
<td>Fixed, U-arm design, dedicated chest unit</td>
<td>Canon CXDI flat panel, high resolution, 125 μm pixel pitch</td>
<td>Capacity powered x-ray generator (220 V), external battery pack with 6 hours backup</td>
<td>Suitable for mobile installations, comes with picture archival communication system (PACS) and dedicated TB viewer software</td>
</tr>
<tr>
<td>Xplorer 1500 Imaging Dynamics Company, Canada</td>
<td>Fixed, dedicated chest unit</td>
<td>CCD or flat panel both available, wireless feature (optional)</td>
<td>Generator-powered with 110 V battery or 380/480 V AC 3-phase supply</td>
<td>User-friendly PACS, capable of mobile installation</td>
</tr>
<tr>
<td>DC Choice Del Medical, USA</td>
<td>Fixed, dedicated chest unit</td>
<td>T-Series = wired detector powered by Toshiba; E-Series = wireless powered by Thales, 148 μm pixel pitch</td>
<td>Customized versions available for generator, for a recommended fix panel no battery required, for wireless solution battery backup is needed in the digital panel</td>
<td>User-friendly PACS, capable of mobile installation</td>
</tr>
<tr>
<td>Eco View9 Chest Exam Ecoray</td>
<td>Dedicated chest equipment</td>
<td>Flat panel detector technology, wireless options with 3.5 to 4 hours battery life</td>
<td>Customized high-frequency generator options, usually 220 V AC 50/60 Hz single phase, 380 V AC 50/60 Hz 3-phase</td>
<td>Mobile installation compatibility, automatic exposure control</td>
</tr>
<tr>
<td>Chiro System CONTROL X-MEDICAL</td>
<td>Dedicated chest unit</td>
<td>Single flat panel DR technology, pixel pitch 143 μm, AC and DC power options</td>
<td>Customized generator options are available with battery backup</td>
<td>Mobile installation compatibility, electromagnetic lock, easy operational design</td>
</tr>
<tr>
<td>ddRElement Swissray</td>
<td>Fixed U arm design, Dedicated chest unit</td>
<td>Single a-Si TFT + photodiode plate, CsI scintillator, 148 μm pixel pitch</td>
<td>Customized high-voltage generator available, max. power 1000 mA Line voltage – 400 V AC±10% 3-phase</td>
<td>Mobile installation compatibility, robust design</td>
</tr>
</tbody>
</table>
Easy DR Digital X-ray (Delft Imaging Systems)
The Easy DR digital x-ray machine from Delft Imaging system offers a complete solution for the purpose of chest radiography. It is specifically tailored for TB diagnostics, as it comes with a dedicated TB viewer. Delft has a history of being associated with chest imaging as the inventor of the Odelca low-dose chest screening camera system, which was widely used in the 1960s. The main component of its DR system is the CANON CXDI flat panel detector. It is available with an external battery pack that provides up to six hours of continuous operation. Delft also offers a package deal to include picture archival communication system (PACS) software and dedicated TB viewer software.

Figure 9: Easy DR x-ray machine from Delft Imaging Systems

Xplorer 1500 (Imaging Dynamics Company)
Xplorer 1500 is a complete DR solution offered by Imaging Dynamics Company. It is a fixed type dedicated chest unit and can be installed within a small space. The unit includes a chest bucky capable of performing radiography on all body sizes. The detector choice is CCD or flat panel, and wireless options are also available. The detector specifications satisfy quality assurance parameters desired for chest imaging. The CCD detector can be 16 mega-pixels 4.6 lp/mm 108 μm or 9 mega-pixels 3.4 lp/mm 144 μm. DQE on CCD is 55%, while on FPDs it is 72%. The system comes with acquisition software Magellan.
DCElite (Del Medical, Inc)
Del Medical offers two varieties of digital direct chest x-ray systems. One model consists of a 3k x 3k, 9 megapixel array with 3.1 lp/mm resolution, while the second model offers a 4k x 4k, 16 megapixel array with 4.1 lp/mm resolution. Both can be suitable for TB diagnostics. These two systems are fully digital, and available as both wired and wireless. It should be noted that for a dedicated chest unit, a fixed panel is recommended. The detectors used are high performance, with the T-Series being the wired detectors powered by Toshiba, and the E-Series being the wireless option powered by Thales.²¹
EcoView9 Chest Exam (Ecoray)
EcoView9 Chest Exam is the full digital x-ray system offered by ECORAY that has the potential to become the equipment of choice for TB diagnostic projects. This model offers easy installation and operation in a limited space such as a clinic or a vehicle. One touch movement by foot switch (auto tracking mechanism) is also available. The flat panel detector technology offers excellent image quality for diagnostic purposes. Designed for chest studies, it is motorized and has a synchronization function between the 17x17 in detector and x-ray tube to offer high workflow productivity.22 A 14x17 detector wired portable version is also available.

![EcoView9 Chest x-ray unit by ECORAY](image)

**Figure 12:** EcoView 9 Chest x-ray unit by ECORAY

Chiro System (CONTROL-X MEDICAL)
The CHIRO-PRACTICAL Radiographic System from CONTROL-X MEDICAL is a simple, reliable complete DR system for dedicated chiropractic/chest imaging rooms. A simplified imaging system, it requires less space, making it appropriate for peripheral hospitals/health care facilities in LMICs.23 The bucky system is equipped with single flat panel DR technology that is designed to meet the high-performance demand of most settings by employing the latest technology in generators, utilizing versatile and durable hospital-grade quality components.23 The extended vertical movement of the tube and the wall stand supports examinations on patients with various anatomical characteristics.
**ddRElement (Swissray)**

*ddRElement* is a Swiss-made product. The system is a space efficient, direct digital radiography set-up that performs all general radiography examinations including chest imaging. Key components – such as mechanics, pillar and arm – are built to last a long time. It features an FP6000 amorphous silicon flat panel detector, a high-voltage generator that delivers a maximum power of 65 KW (80 KW generator also available) and satisfies the needs for working conditions in LMICs. Additionally, it is built in effectively designed shock absorbing housing. Manufacturers say ddRElement has also recently been built for use in vehicles for an “X-Ray on wheels” project. In South Africa, they have several motorized versions of *ddRFormula* (a sister product) in operation. This version, built in trucks and trolleys, has been running very successfully for some years.
Research and development in low-cost x-ray technology

The limited applicability of radiology technology to LMIC settings has proved to be the primary contributor to the limited access of diagnostic imaging services to two-thirds of world’s population. École Polytechnique Fédérale de Lausanne, Switzerland and partner organizations have recently developed a digital x-ray system (GlobalDiagnostiX) to address the needs of LMICs. The product claims to match the performance of standard digital x-ray machines on the market and is ten times less expensive than comparable designs when factoring in related equipment maintenance costs. The product was launched on March 9, 2015 and is yet to enter the commercial market on a global scale. Such a system has the potential to have a major impact on TB diagnostics if introduced with a suitable CAD solution.
Section 6: Readout Solutions /CAD Market Landscape

There is consensus among the global scientific community on a shared concern of inter-reader variability related to diagnosis of TB by chest x-ray interpretation. Advancements in computer science, hardware and software solutions have triggered the development of computer-aided detection of several physiological and pathological conditions including TB, which has promise in supporting mass screening programmes for the disease in high-burden settings, such as LMICs.

CAD developers are working on the development of new solutions and validation of their product through scientific studies and publishing efforts. Unfortunately, the current market for CAD technology is limited with regards to TB detection. That being said, there are some solutions that have been validated by
scientific studies in countries with high TB burden in which select CAD solutions have shown indirect support for TB screening efforts.

**CAD4TB**

CAD4TB is software designed for automated detection of TB for use with digitized CXR images. It has been developed by the Diagnostic Image Analysis Group (DIAG), associated with the Department of Radiology at the Radboud University Medical Centre, Netherlands. DIAG develops computer algorithms to aid clinicians with the interpretation of medical images and thereby improve the diagnostic process.\(^{26}\)

DIAG, in conjunction with Delft Imaging Systems, developed the prototype for the CAD4TB programme in 2001 and, through research grant funding, was able to establish the CAD4TB project with partners in South Africa at the University of Cape Town Lung Institute and in Zambia at the NGO Zambart.\(^ {27}\)

The CAD4TB system consists of a number of individual detection systems for detecting various abnormal and normal pathophysiologic changes suggestive of TB. Such pathophysiologic changes can include: diffuse textural patterns, focal patterns (such as small opacifications), distortions of the lung shape, pleural fluid, blunt costophrenic angles, lymphadenopathy and cavities.\(^{26}\) These systems are trained with examples from thousands of radiographs using machine-learning techniques. Finally, the output of these subsystems are combined to provide a score between 0 and 100 indicating the likelihood that the subject on the image has active TB.\(^{26}\)

![Figure 16: Small lesion in right lung and corresponding detection by CAD4TB in left image (Image source: DIAG)]
CAD4TB has evolved over time, continuously being developed and improved. It is currently at its peak performance level and soon expected to receive CE certification.\textsuperscript{27} Currently, studies that evaluate its effectiveness in Gambia, Tanzania, Pakistan, South Africa and Philippines are underway.\textsuperscript{27}

Three studies have been conducted in Africa since 2007 and have shown a promising future for CAD4TB, especially for mass screening purposes in LMICs where an expert reader is unlikely to be available to interpret CXRs.\textsuperscript{24,28,29} The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CXR compared to Xpert have been reported to be 100\% (95\% CI 96.2–100), 23.2\% (95\% CI 18.2–28.9), 33.0\% (95\% CI 27.6–38.7) and 100\% (95\% CI 93.9–100), respectively. No study that has been performed independent of the test developer has been published to date. Furthermore, no study is currently available that assessed the ability of the software to differentiate non-TB abnormal (e.g. pneumonia or malignancy) and normal, which represents a key added value beyond the diagnosis of TB of CXR as a diagnostic tool.

CAD4TB can be used with digital CXR imaging from either CR or DR technology. The joint venture project of the Diagnostic Image Analysis Group (DIAG) and Delft Imaging System in the Netherlands promises a complete solution with the easy DR x-ray system, paired with the CAD4TB software, specifically developed for use in LMICs.

**DigiportXCAD**

Software consulting MVIP (Germany) and consulting GmbH are also developing a CAD System for lung pathologies (DigiportXCAD).\textsuperscript{30} The project partners include Medex Loncin S.A. (Lüttich), Damien Foundation (Brussels), DZK Zentralkomitee zur Bekämpfung der Tuberkulose (Berlin) and HAWK Hochschule für angewandte Wissenschaft und Kunst (Göttingen).\textsuperscript{30} The project also includes the development of DigiportX TB, which is an ultra-portable digital CXR from Medex Loncin S.A. (Belgium). The system is currently being evaluated in Bangladesh with the Damien Foundation.\textsuperscript{31} Limited information is currently available, but the project is expected to grow over the next couple of years.

**ClearRead**

Riverain Technologies (USA) have developed some useful CADs for lung imaging which may have indirect implications for TB diagnostics (though none are specific for TB).\textsuperscript{32} ClearRead Bone Suppression increases the clarity of chest X-rays by suppressing bone on digital images and revealing the soft tissue. Similarly, ClearRead Detect identifies areas on a chest x-ray that may be early-stage lung cancer, which can be applicable for TB as well. ClearRead Compare illustrates density changes between current and prior chest X-ray images which can also have significant impact on monitoring TB treatment.
None of these applications are dedicated to TB and they still require an expert to read the images (unlike CAD4TB). Nevertheless, there are benefits of utilizing the software to support radiologists/radiographers with limited skills and experience.

Section 7: Discussion

The market dynamics of digital radiology solutions for TB are complex due to a number of contributing factors. A cocktail of technologies required to work seamlessly together (detector technology, x-ray source, computerized readout solutions) is one of the prime challenges. Furthermore, from a business perspective the TB diagnostics market is not a priority for the radiology industry, as end-users of such technology are mostly based in resource-limited settings of LMICs.

Currently available technology solutions are capable of producing high-quality diagnostic chest x-rays. It has been noted that CXR solutions can be obtained by a variety of x-ray machine types, but a complete, compact, digital machine that can be deployed in LMICs would be optimal.

Most of the systems mentioned here are robust in design, provided with alternative power back-up and require fairly small amounts of space for installation (potentially even within vehicles for outreach to rural clinics). Cost drivers are detector components, which amount to an average of 50-60% of the total equipment cost. The market landscape of detector technology has been analysed and a list of available products for digital radiography from leading detector manufacturers has been provided in this report.

CAD solutions for TB diagnostics are currently in an early phase. Despite tremendous developments in the area of CAD solutions in diagnostic radiology, developers are more interested in products that can be used in conjunction with advance imaging modalities such as computerized tomography (CT)/ magnetic resonance imaging (MRI) for screening of several chronic diseases of concern, such as cancer (colon, lung, breast and prostate). There is a range of screening CADs available for mammography and CT colonoscopy, whereas only one complete CAD is dedicated to tuberculosis (CAD4TB).

There is significant market potential for a compact, robust and fully digital chest x-ray system coupled with a dedicated CAD for screening purposes. However, very few manufacturers are able to offer this combination of imaging features. A low-cost, high-quality detector system packaged within a sturdy chest x-ray system and with a reliable CAD solution dedicated to TB diagnostics could be the turning point for establishing the role of chest radiography for mass screening of TB in high burden settings.
Section 8: Conclusion

The current market for radiology solutions offers very limited choice in terms of full digital chest x-ray systems suitable for use in LMICs. Most of the systems available are complex in design. The cost of digital detector technology remains the single most important limiting factor for implementation of such technology to achieve the more widespread use of high-quality radiography for TB diagnosis.

There is only one dedicated readout solution (CAD4TB) for interpreting chest x-rays and it can be used with all forms of digital chest x-ray images. CAD4TB has evolved over time. However, studies to date are limited to developer-driven assessments in Africa.
References


