



**WHO RECOMMENDATIONS
AND DEVELOPMENTS IN THE**

PREQUALIFICATION OF CHEST RADIOGRAPHY AND COMPUTER-AIDED DETECTION (CXR-CAD) FOR TUBERCULOSIS

**8TH MARCH
2023**

OVERVIEW

The past few years have seen an unexpected increase in the number of tuberculosis (TB) cases and deaths globally.

This rise is a reversal of decades of progress in the field and is attributable in many ways to the COVID-19 pandemic. **In 2021, 10.6 million people worldwide contracted TB and 1.6 million people died from the disease.** Sadly, about 40% of people who had TB in 2021 are not known to have been diagnosed or treated. Improving access to diagnostics in order to avoid these preventable TB deaths therefore remains a key priority.

Chest radiography (CXR) is a highly sensitive tool for triage and screening for TB.

However, the shortage of trained CXR readers, particularly in countries with a high TB burden, remains a barrier to its widespread use for TB detection. Much work has been done in recent years to support the development and validation of computer-aided detection (CAD) software for CXR, which has real potential to increase access to TB screening. In 2021, based on data showing that available CXR-CAD tools provided equal or improved accuracy compared with human readers, the World Health Organization (WHO) updated their TB guidelines to recommend the use of CXR-CAD for TB triage and screening in adults. While implementation of these tools is likely to be transformative in the field of TB, appropriate quality assurance will be required to ensure their continued accuracy and safety in community settings.

FIND recently convened policy makers, developers, and procurers of CXR-CAD software to discuss ways in which these tools should be evaluated and approved for use in the TB field, with a focus on developments in the CXR-CAD WHO prequalification (PQ) pathway. The hybrid meeting on 8 March 2023 featured: a summary of the current WHO recommendations, implementation considerations, and priorities for the future of CAD in TB screening and triage activities; an introduction to the PQ process for assessment of CAD products in development; and an overview of the FIND Validation Platform and process for evaluation of CXR-CAD software performance at FIND. Representatives from USAID, The Global Fund and Global Drug Facility explained the requirements for CXR-CAD products from a procurement perspective and a digital health specialist from UNOPS/Stop TB Partnership drew the meeting to a close with an encouraging presentation on future directions and potential in the CXR-CAD field.

KEY TAKEAWAYS

>>>> 01

The use of CXR-CAD technology in the triage and screening of TB, now recommended by the WHO, is cutting-edge and will be associated with unique regulatory challenges.

>>>> 02

WHO PQ will be a robust quality assurance process, that follows good regulatory principles to ensure accuracy and safety of CXR-CAD products for use in TB detection in the field, and will positively influence uptake in low resource settings.

>>>> 03

The technical specification series (TSS) for WHO PQ is under development, and finalisation will require a collaborative approach with input from all partners including health systems, providers and patients, procurers, implementors, CXR-CAD software developers and CXR manufacturers.

>>>> 04

CXR-CAD technology is still rapidly evolving and there is great potential for future expansion into vulnerable patient subgroups and non-TB indications.

>>>> 05

There is a willingness among all CXR-CAD stakeholders to work together to determine how best to evaluate CXR-CAD products to ensure optimal performance as well as support ongoing innovation.

COVER IMAGE CREDIT: FRIENDS FOR INTERNATIONAL TB RELIEF (FIT), VIET NAM

AGENDA

MODERATOR

Cassandra Kelly-Cirino,
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INTRODUCTION

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CEO, FIND

POLICY PATHWAY FOR TB CADs

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WHO PREQUALIFICATION (PQ) FOR TB CAD: AN OUTLINE OF THE PROCESS AND TIMELINES

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Unit Head Prequalification Unit (PQT) of the Regulation & Prequalification Department, WHO

TECHNICAL SPECIFICATIONS APPROACH: EXPECTED CRITERIA AND PARAMETERS FOR TB CAD

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THE PROCURER'S PERSPECTIVE FOR TB CAD

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Grania Brigden
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FUTURE DIRECTIONS

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Digital health specialist at UNOPS/Stop

IMAGE CREDIT: TILA T.M. MANUGA



” ‘Systematic screening is critical to ensure we can detect TB early in the people who need it, while also identifying people who could benefit from TB preventive treatment’

Cecily Miller, WHO GTB

»»»»» **IN 2021, THE WHO INCLUDED CXR-CAD IN THEIR TB SCREENING RECOMMENDATIONS, MARKING THE FIRST WHO APPROVAL OF AN ARTIFICIAL INTELLIGENCE (AI) TOOL FOR CLINICAL USE**

As part of the WHO TB guideline development process, three CXR-CAD products were assessed for TB screening and triage use cases. These products achieved equal or superior accuracy to human readers, with similar or reduced variability and, as a result of these findings, WHO included the following recommendation in its 2021 TB guidelines:

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.

Conditional recommendation, low certainty of evidence

FROM THE WHO CONSOLIDATED GUIDELINES ON TUBERCULOSIS.
MODULE 2: SCREENING – SYSTEMATIC SCREENING FOR TUBERCULOSIS DISEASE. 2021

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	0.90-0.92	0.25-0.79
CXR with human reader	0.89-0.96	0.36-0.63



IMAGE CREDIT: MICHAEL CAIRNIE/MIXRAY

➤➤➤➤ **CXR-CAD MAY BE USED DIFFERENTLY FOR TB DETECTION IN THE FIELD AND IN THE CLINICAL SETTING**

Using CXR-CAD for TB detection is likely to reduce workload for human readers by identifying images with abnormalities that are potentially TB related to determine which patients need further diagnostic evaluations, as well as deprioritizing images without any abnormalities, allowing radiologists to focus on more difficult cases. Additionally, CXR-CAD can be used as a diagnostic aid to cross check images that have been read as normal and abnormal by a trained health worker.

➤➤➤➤ **IMPLEMENTATION OF CXR-CAD IN A NEW SETTING CAN BE CHALLENGING BUT SUPPORTIVE TOOLS USING AVAILABLE CLINICAL DATASETS ARE USEFUL TO ASSIST WITH CALIBRATION AND ASSESS PERFORMANCE**

The WHO calibration toolkit is available to support implementation of CXR-CAD. It includes a study protocol through which an operational study designed to help calibrate CXR-CAD can be performed, as well as a web-based data analysis tool which uses data from the calibration study to calculate the sensitivity, specificity, associated yield and cost of screening across a range of thresholds in that particular setting, allowing the user to select which threshold best serves their needs for screening. The WHO is currently working to increase the available clinical data and to clarify best available approaches to establish the abnormality threshold, to facilitate the implementation of CXR-CAD in new settings.



‘WHO PQ has become a trusted and reputed symbol for safety, quality and efficacy across stakeholders.’

Deusdedit Mubangizi, WHO PQ



IN RESPONSE TO THE WHO RECOMMENDATION FOR CXR-CAD IN TB, DEVELOPMENT OF A WHO PRE-QUALIFICATION (PQ) PROCESS WAS INITIATED TO EVALUATE INDIVIDUAL CXR-CAD PRODUCTS

WHO PQ evaluation will include an extensive dossier assessment and a manufacturing site inspection, as well as other product-specific elements. The application will need to provide a thorough description of the product, its safety and performance, its design, and the associated quality management system. The WHO PQ process will take into consideration third-party assessments of a CXR-CAD product. The outcome of the PQ assessment will be publicly available in the form of WHO public assessment and public inspection reports.



THE TSS FOR CXR-CAD PRODUCTS IS CURRENTLY IN DEVELOPMENT

The TSS will set out a comprehensive description of the criteria that will be used to evaluate CXR-CAD products during the WHO PQ process and provide information on the minimum requirements that should be met by developers and manufacturers. It will include requirements for software design and development, hazard analysis and risk management, essential principles, and validation and verification of the product. The context in which the product will be implemented will form a critical part of the PQ evaluation.



FINALISATION OF THE TSS FOR CXR-CAD PRODUCTS WILL REQUIRE A COLLABORATIVE APPROACH

The first version of the TSS is expected to be available for public consultation by mid-April 2023, with a final version published in June. A collaborative approach between policy makers, developers and manufacturers is required before TSS finalisation to ensure all relevant aspects of CXR-CAD product evaluation are considered.





IMAGE CREDIT: BEN PHILIPS/FIND

➤➤➤➤ **AN EFFICIENT WHO PQ PROCESS DEPENDS ON A GOOD QUALITY APPLICATION**

Providing a comprehensive, high-quality, well-presented, well-structured dossier at submission and promptly delivering thorough responses to queries throughout the WHO PQ process will facilitate timely assessment of a CXR-CAD product. Early engagement with the PQ team is useful to ensure a detailed understanding of all available guidance prior to submission.

➤➤➤➤ **GIVEN THE OPPORTUNITIES FOR CONTINUOUS IMPROVEMENT IN AI TECHNOLOGIES, A ROBUST QUALITY MANAGEMENT SYSTEM IS ESSENTIAL**

Monitoring and assessment of continuously improving software versions is a particular complexity for CXR-CAD products as AI tools. As such, a solid quality management system is required to mitigate risks and ensure that evolving products still perform as intended. While software upgrades considered to be significant for WHO PQ will likely be in line with global regulatory norms and accepted standards, this is still an area of active discussion with regards to TSS finalisation. However, it is already clear that consideration of software version control should underlie all elements of the WHO PQ dossier.



‘FIND is driven by one goal – to ensure equitable access to health, driven by equitable access to testing.’

Bill Rodriguez, FIND



FIND IS RESPONSIBLE FOR THE INDEPENDENT PERFORMANCE EVALUATION OF CXR-CAD PRODUCTS

The FIND Validation Platform allows rapid, standardised in silico assessment of digital diagnostics and will be used to independently evaluate CXR-CAD product performance as part of the WHO PQ process. The globally representative TB data sets used within the platform include high-quality reference standards as well as digital chest x-rays reviewed by human experts.



THE SOFTWARE ONBOARDING PROCESS ENSURES THAT THE EVALUATION OF CXR-CAD PRODUCTS OCCURS IN A TIMELY MANNER

Product onboarding involves key steps to ensure the virtual environment created is appropriate for the specific software and meets the requirements of the software developer for the use of their product. Additionally, the evaluation is conducted in a manner that prevents the CXR-CAD software developers from accessing the evaluation datasets to mitigate any risks of the AI algorithms getting trained on these datasets. Lastly, the performance reports are generated in a standardised, automated manner to ensure quick availability of the performance data.



THE CLINICAL PERFORMANCE OF CXR-CAD PRODUCTS IS EVALUATED FOR THE SCREENING AND TRIAGE USE CASES APPROVED BY THE WHO

The FIND Validation Platform tests if performance of the CXR-CAD product in screening and triage use cases is non-inferior to the standards established by the WHO during the guideline development process in 2020. Additionally, the evaluation will include other clinical performance measures and assessment in patient subgroups with differing age, gender, HIV status, TB history and WHO region. Two additional datasets assessing repeatability and error handling will also be included. A standardised report of performance assessment will inform the WHO PQ outcome.



EXPANDING THE BODY OF HIGH-QUALITY CLINICAL DATA IS CRUCIAL TO ENSURE BROAD APPLICABILITY OF CXR-CAD PRODUCTS

FIND is proactively expanding its archives of high-quality images to facilitate assessment of CXR-CAD product performance for new use cases including paediatric TB, TB in people living with HIV, and non-TB indications such as pneumonia and COVID-19. Assessment of products in these areas will support decision-making for future WHO recommendations.

‘CXR-CAD products are developing fast, which ask for quick but independent performance evaluations of new products and versions. That’s why FIND has setup a Validation Platform.’

Sandra Kik, FIND

➤➤➤➤ **SPECIFIC CRITERIA MUST BE MET IN ORDER FOR GLOBAL FUND TO PROCURE CXR-CAD PRODUCTS**

For procurement by Global Fund, CXR-CAD products must have either WHO PQ, authorisation for use by one of the stringent regulatory authorities of the founding members of the global harmonization task force (GHTF), namely EU, USA, Canada, Australia and Japan, or acceptability for procurement using grant funds, as determined by the Global Fund based on the advice of the Expert Review Panel.

➤➤➤➤ **SIMILAR QUALITY-ASSURANCE CRITERIA MUST BE MET TO BE ELIGIBLE FOR PROCUREMENT VIA THE GLOBAL DRUG FACILITY**

For the Global Drug Facility, the largest procurer of quality-assured TB products for the public sector globally, quality assurance requirements are three-fold. First, the product must either be 1) recommended by the WHO Global TB Programme, or 2) have regulatory approval by a founding member of the GHTF (as above), or 3) have WHO PQ, or 4) have a Conformity Assessment Body (CAB) certificate, and must also have a declaration of conformity in accordance with the International Medical Device Regulators Forum and/or ISO 17050. Additionally, manufacturers/developers must have a valid quality management system to ISO 13485 (or equivalent) and be assessed by a competent CAB recognised by the regulatory authority of a founding member of the GHTF. Finally, the supplier (if different from the manufacturer/developer) must have a valid and certified quality management system per current versions of ISO 9001 (or equivalent). For products and suppliers that meet these QA criteria, they must then successfully compete in a GDF international public tender (e.g., meet all the technical and financial specifications) to be included in the GDF catalogue. GDF takes a catalogue approach to including suppliers, aiming to have multiple suppliers and products whenever possible, to provide options to TB programmes to choose products that work best for their country context.

➤➤➤➤ **PROCUREMENT BODIES EMPHASISED THE IMPORTANCE OF WHO PQ FOR CXR-CAD**

For procurers, WHO PQ for CXR-CAD products is incredibly important to support decision-making as it provides assurance that these products meet minimum performance standards in TB specifically (as set out in the TSS), which other regulators are generally not yet doing.

” ‘CAD technology is going to evolve very quickly outside of TB, it’s already evolved. So, it’s another call to action to all of us to determine how we can work together collaboratively.’

Zhi Zhen Qin, Stop TB Partnership

»»»» **EARLY USER FEEDBACK ON USE OF CXR-CAD IN THE TB FIELD IS POSITIVE**

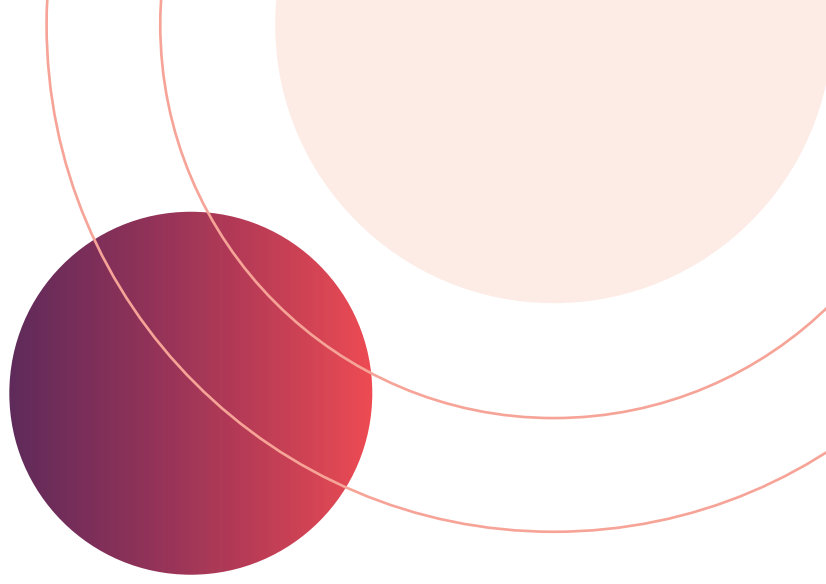
A recent CXR-CAD user survey conducted by Stop TB’s DHT Hub found that users were pleased with the high throughput, accurate nature of the CXR-CAD tools as well as the reduced turnaround times.

»»»» **CXR-CAD USERS HAVE HIGHLIGHTED SEVERAL AREAS FOR FUTURE IMPROVEMENT**

While feedback from early CXR-CAD users was positive overall, a number of areas requiring improvement were noted. These included the ability to identify a broader array of abnormalities with CXR-CAD, suggestive of pathologies other than TB, as well as the need to read CXRs capturing other views in addition to the posterior-anterior plane. In line with the WHO and FIND’s areas for development, better evidence to improve detection of TB in older adults, and expand recommendations for use to children were raised as specific needs. Importantly, a requirement for improved understanding of threshold selection and results interpretation was also noted, with the need for an iterative approach with novel datasets to improve CXR-CAD performance in these areas discussed.

»»»» **THERE IS ENORMOUS POTENTIAL FOR EXPANSION OF CXR-CAD USE IN THE FUTURE, BOTH IN THE TB FIELD AND IN A WIDER HEALTHCARE SETTING**

CXR-CAD technology is young and still rapidly evolving, but it holds enormous potential in the differential diagnosis of lung disease the future. Improvement in health equity is possible through innovative development of algorithms for CXR-CAD use in marginalized populations. In addition, there is the potential to provide precision diagnosis through machine learning algorithms using a large variety of data sources. Finally, integration of CXR-CAD findings with electronic medical records would greatly improve the efficiency of diagnosis and better inform decisions on treatment.



➤➤➤➤ **WIDESPREAD COLLABORATION IS REQUIRED TO REALISE THE POTENTIAL OF CXR-CAD IN GLOBAL PULMONARY HEALTH**

As CXR-CAD evolves, there will be lessons for all stakeholders, including policy makers. To ensure the full potential of CXR-CAD is realised, collaboration among all stakeholders will be needed to facilitate access to novel clinical datasets which can be used to improve product performance in a broad variety of populations globally and to build consensus on appropriate reference standards for conditions other than TB.



IMAGE CREDIT: BEN PHILLIPS/PIND



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