eRx – A Technological Advance to Speed-up TB Diagnostics

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Abstract

In 2016 an interdisciplinary collaborative research team started an ambitious project to assist the diagnosis of tuberculosis (TB) in areas with over-burdened and poor healthcare infrastructure in the outskirts of Lima, capital of Peru. Currently we have implemented an integrated system which connects nurses, physicians and scientists, in a network of cooperation to identify and report TB cases. Our Electronic Mobile system (called 'eRx') is a tool that can be used by local nurses in the healthcare centers which allows them to send X-rays along with additional prospect patient information, directly to be evaluated by a physician who is located at a different location. The physician has then access to a web-based system that can be accessed using a computer or a tablet which allows him/her to evaluate the data coming from the distinct healthcare centers. The physician may also be assisted by a Beta version of an automatic diagnostic software which uses Deep Learning to identify the presence of lung abnormalities as well as the possible manifestations for TB. The goal of our research is to reduce patient waiting times to be diagnosed with TB by implementing a socio-technical solution to optimize the diagnosis process.
To support future developments of the automatic diagnostic software, we rely on another web-based platform which contains over 10000 X-rays images which are being annotated by a specialist who provides the regions where the TB manifestations can be found, which will be used later to train a Region-Based Convolution Neural Network. The software for the eRx system covers the obtaining of high-quality data, artificial intelligence support and mobile technologies directly in hands of the healthcare professionals, each software has already been validated individually, and will be evaluated together during a pilot study working directly with local healthcare centers, physicians and nurses. Our study has approval from the Peru National Institute of Health and the IRB Board from the School of Medicine at Universidad Cayetano Heredia.

Keywords: tuberculosis; diagnosis; deep learning; deep convolutional neural networks; mHealth; Peru.

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1. Introduction

Tuberculosis (TB) is a potentially serious infectious bacterial disease which usually affects the lungs, it is partially preventable by vaccine and it is treatable with antibiotics, even so, it remains a major cause of death globally. The disease is airborne spreading and affects mainly disadvantaged populations. In 2017, according to the 2018 Global Tuberculosis Report by the World Health Organization, 10 million people developed TB, two thirds were in India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa and caused an estimated 1.3 million deaths worldwide [1]. 95% of the deaths occurred in countries with low and middle income [2]. In the Americas, Peru has the highest incidence per capita, including virulent multi-drug resistant and extensively drug resistant strains [3].

The scientific community has tried to improve the TB diagnostic and treatment in several ways. Ekins et al. [4] developed a machine learning algorithm to test 639 known compounds against the known inhibitors from the resistant bacteria pursuing to find a docking model in which a specific sample of the bacteria is sensitive to a set of drugs, with promising results. Mani et al. [5] created a microchip based technology to identify rapidly the presence of anti-mycobacterial IgG in the plasma and so, identify if there is an active TB or a latent infection with a sensitivity of 72%. Convolutional Neural Networks (CNNs) also have been employed analysing chest radiography of TB suspect patients, Lakhani and Sundaram (2017)[6] developed an automated classification of pulmonary TB using CNNs where they claim a sensitivity of 97.3% and specificity of 100%. In addition, the classifier could be improved using more than one architecture and using a radiologist-augmented approach [6].

Low-and Middle-Income Countries (LMICs) usually have persistent social inequalities in health, a limited number of local healthcare professionals, and weak healthcare infrastructure, making TB challenging to be diagnosed and treated. The global health community has confronted the situation by focusing on developing and testing effective vaccines, improving the diagnosis process, and enhancing patient adherence to the medical treatment.

It is critical to reduce the TB diagnosis delay in mitigating disease transmission and minimizing the reproductive rate of the TB epidemic. The goal of this research is to reduce patient waiting time for diagnoses by developing a socio-technical solution to the TB diagnostics problem. Specifically, we aim to design a user-centred, mobile device-based computing system to expedite the TB diagnosis process by developing and implementing image processing and machine learning techniques to analyse patients' chest X-ray images.

This paper goes thorough this entire process detailing the situation of the healthcare in LMICs, a case study about the situation in Lima, Peru at the Tupac Amaru Health Network, the technological approaches which we developed to address some of the issues, an applied study model considering the technologies and the healthcare system, the discussion about the current situation and the direction of our research, and finally conclusions about the theme.

2. Background

2.1. Mobile Computing in Healthcare (mHealth)

Point of care delivery is critical for the success of any application in the clinical healthcare environment. In Peru, as in many developing countries, a mobile device-based computing solution is very suitable within the context of resource-poor communities. The unique characteristics of the mobile devices, such as the pervasiveness and low cost, provide them the opportunity to support and enable smart care decision making in a connected health scenario for automatic health scenario and tuberculosis screening.

- *mHealth in Peru:* In a recent review of the mHealth literature published in Perú, Ruiz et al. [7] showed that mobile health interventions have enormous potential to improve access and the quality of health services in Peru, increasing the effectiveness of public health programs and reducing healthcare costs [7]. Out of 19 papers selected, most of them showed positive impacts, and four were about tuberculosis. It is important to notice that most of them were implemented as pilot projects [7].

However, the majority of the papers demonstrated that mobile health interventions are well accepted by the population and well-developed projects might contribute to reduce the gap in public health, reducing limitations such as lack of resources (human and logistic) in heath care centers, high dispersion of the population and lack of infrastructure (roads, transportation and Internet connectivity).

- *mHealth for TB Diagnostics:* During the last few years, mobile phones have been successfully used for diagnosis of tuberculosis [8]. In Peru, Zimic et al. [9] proposed a relatively minimal investment with mobile phones to facilitate the diagnosis of tuberculosis using a low cost Microscopic Observation Drug Susceptibility (MODS) in remote settings where a lack of trained personnel may otherwise be a limitation [9]. Nowadays, with the advances in mobile processors' computing ability, images taken by a cellphone can be immediately processed and analyzed with the help of computer graphics algorithms. Today's global wireless infrastructure also allows transmission of a wide variety of tuberculosis images (such as X-rays) to remote locations for telemedicine diagnosis. Therefore ubiquitous cell-phone based applications can provide unique opportunities to combat tuberculosis, especially in developing countries [10]. Schwartz et al. [11] assessed the diagnostic accuracy of digital photographs of plain film chest X-rays obtained using a mobile phone in Botswana. The authors concluded that digital photographs of chest X-rays obtained via a mobile phone equipped with a digital camera are comparable to plain film chest X-rays [11].
- *The need of a timely tuberculosis diagnosis in Peru:* Tuberculosis remains as a serious public health problem. A successful treatment plan requires a proper diagnosis, in addition to good knowledge about drug susceptibility [12]. Reducing the tuberculosis diagnosis delay is critical in mitigating disease transmission and minimizing the reproductive rate of the tuberculosis epidemic. Different factors impact delays in tuberculosis diagnosis [13], such as: patient health seeking behavior, healthcare centers with poor infrastructure and equipment, inadequate resources and information systems (mostly paper-based), lack of (or inexistent) documented processes, and lack of human resources as part of a multidisciplinary tuberculosis team.

2.2. Computer-aided System to Screen the Chest Radiography Image for TB Diagnosis

The research activities in computer-aided image analysis for TB screening from X-ray images can be broadly divided into two categories: (1) the first category is the computer-aided screening and scoring algorithms using chest radiographic features for the TB diagnosis [14-21]. Research activities in this category focus on developing different types of visual features and classification algorithms to score and screen different types of TB manifestations. Most of the papers employ texture features (e.g., Local binary patterns (LBP) [22, 23], Daubechies wavelets [24]) or geometry features (e.g., circularity, Hessian shape features) [25, 26]. The classification algorithms employed in these papers range from simple threshold-based approach or k-nearest neighbors (K-NN) algorithm to more complicated methods, such as Decision tree and Support Vector Machine (SVM); (2) the second category of related work focuses on X-ray image categorization on the organ and pathology level [27]. The mainstream methodology in this area is based on local patch representation of the image content (e.g., visual bag of words (Visual BoW) approach). This type of dense sampling of simple features are then feed to a non-linear kernel-based classifier, such as SVM classifier. The goal is to discriminate between healthy and pathological cases. It is also shown that this type of methods can successfully identify specific pathologies in a set of chest radiographs.

3. Technological approaches developed

3.1. Building an annotated lungs X-ray dataset

There is an effort in TB screening tests on developing countries [28, 29], but, to the best of our knowledge, there is no publicly available large-scale, annotated X-ray image dataset. Most of the existing research [14-21, 27] in computer-aided TB screening employ small datasets for evaluation and validation. Most of the datasets have less than 200 images [30]. There are a few large datasets, such as ImageCLEF [31], JSRT Digital Image Database [32], and ANODE Grand Challenge Database [33], with over tens of thousands images. However, they include only one or two aspects of TB manifestations (e.g., pulmonary nodule). Without a large-scale data set with reliable annotation, it is difficult to determine the accuracy of existing and proposed approach when applied to real-world clinic data. Furthermore, any new dataset demands an accurate annotation to train a detector of the manifestations individually and might differentiate among many TB manifestations. One way

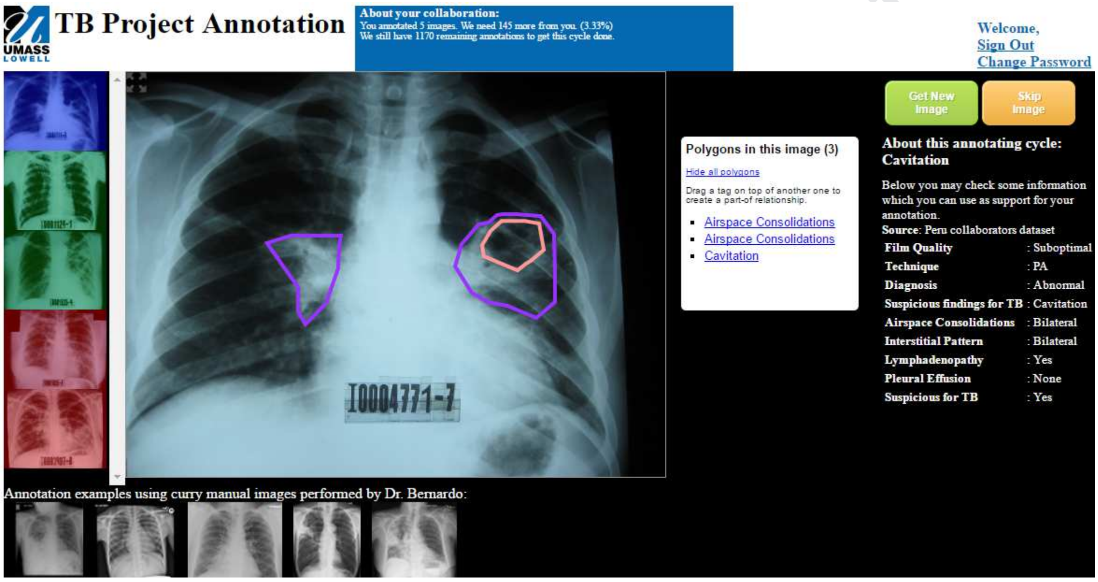

Figure 1: Annotation Software main screen.

to provide this is with the assistance of specialized Physicians to lead and review the annotations and the annotation software itself.

3.2. Annotation software to highlight regions of interest on lungs guided by pulmonologists.

A tough task in Artificial Intelligence applied to Medical Images is showing the computer what in the image indicates the diagnostic. There are some existing efforts of annotation software to medical images [34, 35], however, there is not an open source annotation software dedicated to X-ray images with supporting guidance information. Due the specificity of the software we need, we developed our own annotation software

[36], inspired and using code parts of LabelMe tool [37]. Nevertheless, localizing a TB manifestation and the boundaries is a challenging task even for pulmonologists, therefore, the annotation software can be used only by trained annotators.

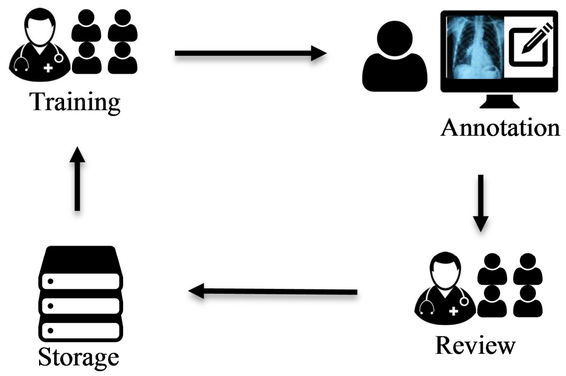

Figure 2: Annotation cycle that repeats for each TB manifestation.

The software is intuitive, its main screen can be seen on Figure 1, the difficulty is in properly identifying the TB manifestations, to make this process easier, a panel shows a complete diagnostic to the current x-ray, indicating the presence of all the TB manifestations. The annotator must look this panel and then draw over the x-ray image a polygon bypassing the corresponding TB manifestation, once done the polygon, the annotator identifies the manifestation, the confidence level of the annotation, and some additional notes (singularities of the current annotation).

The annotation software also lists all the annotator's images on the left panel and all current image's polygons in an easy overview, it also indicates whether the image contains some expected manifestation. The software provides two buttons, one to get a new image and another to skip the current image in case of inability to annotate the current one.

The annotation is possible only under the training and supervision of an experienced pulmonologist or radiologist. Due the variety and complexity of TB manifestations, the annotation process was separated by manifestation and a cycle of training and review was established for each one. The process of a cycle is illustrated on Figure 2, the cycle starts with training with a pulmonologist, followed by the proper annotation for each of the collaborators, after annotating all the images belonging to the cycle, a review session is performed with the pulmonologist. During the review, the images annotated with low confidence are reviewed by the pulmonologist along with the annotators, this process serves not only to correct some wrong annotation but to provide a reinforcement training.

Starting in the second manifestation onwards, when the same image is being annotated again for another manifestation, it also shows the manifestations previously annotated. This helps to avoid equivocation and allows for correcting some previous manifestations annotated with the wrong label. In each cycle, the annotation software informs the status of your current collaboration with how many images remains to be annotated by the team and by his/herself individually.

At the end of the last cycle, all the images contain annotations for all the manifestations we are considering for TB diagnosis. After this step, the data is ready to be processed by a deep learning algorithm.

3.3. Deep learning algorithm to predict TB manifestations

The dataset we used is provided by partners in Health in Peru [38] , it includes 4701 images, where 453 are non-TB lungs and 4248 are TB suspicious coming from Peruvian patients with many distinct manifestations. In this dataset we did some experiments [39] to explore the potential of the dataset plus deep learning techniques.

The first experiment we conducted is the binary categorization. This means our goal is to classify any X-ray TB image into two categories: normal and abnormal. We adapt the GoogleNet model [40] from Caffe [41] as the pre-training model, and we generate a supervised pre-training from ImageNet [42] with more than 14 million images. Then we use 4701 images from our dataset for finetuning, transforming the network to a TB detector. We used 4/5 of the TB images (3760) for training and 1/5 (941) of the images for testing. In our experiments without any preprocessing, we achieved 93.4% of accuracy for binary classification (normal/abnormal). The result is impressive considering that we only used raw pixels.

We performed also an algorithm for multiclass categorization. We use the same GoogleNet model as the previous experiment, and 4/5 of images for training and 1/5 of images for testing as well. But in this experiment, we add more categories named specific TB manifestation. In these experiments, our goal is to classify the TB X-ray images into multiple categories. Each category corresponds to one of the TB manifestations, we picked only the biggest three TB manifestations, Cavitation, Lymphadenopathy, and Infiltration, and grouped all other manifestations into the group Other. In this experiment, we achieve 96.05% of precision (87% to Cavitation, 91% to Lymphadenopathy, 97% to Infiltration and 90% to others)

It is important to discuss a little about sensitivity and specificity in this work, while the first one aim to identify all the positive cases, the second focus in make sure the negative cases are accurate. In this project is critical to identify the positive cases, once they are selected to further tests and skip a very long line of patients. In this analysis the Recall and Miss Rate for each of the manifestations was respectively:

- Cavitation: 94% and 6%
- Lymphadenopathy 98% and 2%
- Infiltration 97% and 3%
- Others 100% and 0%

We do believe that better results may be achieve with a more sophisticated implementation focusing on medical image detection. The X-ray pictures do not have an optimal quality most of the time, increasing the importance of good pre-processing techniques which will be explored in further experiments.

4. Applied Study

The deep learning algorithm has shown promising results encouraging us to develop a pilot study to evaluate the algorithm in a real-world scenario. In the mapping process, some useful information was acquired helping us to understand the needs and plan carefully how to contribute with the existing workflow. The pilot study will be performed in 12 TB clinics belonging to Tupac Amaru Network in Lima, Peru. Currently, when the patient goes to a TB clinic holding the X-ray and other exams and there is no available physician (a very common situation in developing countries), the nurse gets the patient X-rays and along with the exams. The patient medical record is sent to a physician in a hospital or it remains in the TB clinic waiting for a physician visit. When the nurses identify by themselves a very serious condition, they send the X-ray or even pictures to the physician by informal ways by phone messages. A critical factor in the patient care is the time between getting the X-ray and having the X-ray analyzed by a trained healthcare professional.

Facing this specific scenario, we planned a pilot study interfering as little as possible with the existing workflow found at the TB clinics. However, the final decision about the diagnostic still will always be done by the responsible physician. The pilot study has the following goals:

1. Analyse the acceptability of the mobile technologies by the healthcare professionals (nurses and physicians);
2. Verify the quality of images that can be acquired, identify the possibility to the physician in providing the diagnostic based on the images;
3. Calculate the time used since the patient deliver the X-ray and the time to a physician look at it and compare this time with the time the physical X-ray takes;
4. Obtain the accuracy of the Deep Learning algorithm to identify the TB manifestations.
5. Provide valuable information to physicians to aid the diagnostic.

As we did a data survey about the health care system, valuable information was obtained about the entire process since a patient gets in one of the TB clinics, and the workflow containing the exams prescription (X-ray and others). The study currently is focusing on the situation where the X-ray is delivered to the nurse until the moment the diagnostic is provided, during which the health care professionals perform tasks such as uploading X-ray images and patient records to the system. This section is divided in three subsections: *System Input*, *Algorithm Analysis* and *Physician Feedback and Diagnostic*.

4.1. System Input

When the patient returns to the TB clinic holding the X-ray, the patient usually gives it and all other exams to the nurse intending to schedule an appointment with the physician, so, the nurse asks the patients if they are interested in becoming part of the study. If agreed, the nurse takes a photograph of the X-ray and send it to the system where the image will be analysed by deep learning algorithms to identify all the TB manifestations. Figure 3 shows the initial screen of the app with an X-ray already uploaded. Along with the X-ray, the nurse will entry the medical examination and lab results if available.

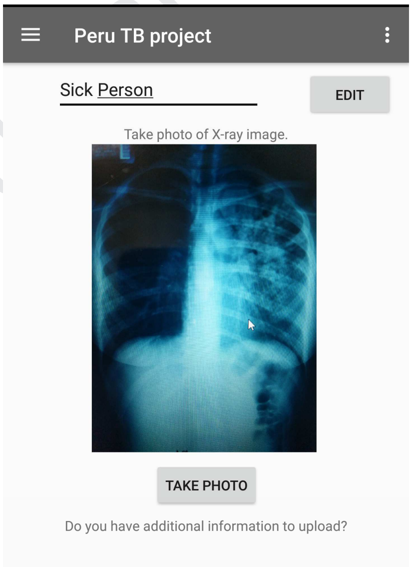

Figure 3: eRx app

4.2. Algorithm Analysis

The workflow for proposed experimental study is presented in Figure 4. The process may vary according with the severity, symptoms, number of patients and physician availability, but in this first study, we intend to insert the mobile application in the most common work flow which is when the patient returns to the TB clinic having his/her X-ray, and there is no physician available, only the nurses, any X-ray prescription occurred before the study take place.

The nurses and physicians are the only people to have contact with the patients, the patients do not have access to the system or to the app. The app only communicates with the nurse and with the physician, but the nurse can only upload images and data to the system, there are limited features the nurse can interact with.

A code is attached to the X-ray picture to identify the patient, but this only can identify the patient into the TB clinics system and only the physician can match the medical record information with the respective patient.

After the image is uploaded into the system, the software immediately starts the analysis to get it ready for the physician. The following 7 manifestations will be tracked: cavitation, lymphadenopathy, pleural effusion, interstitial pattern, miliary disease, ghon focus and alveolar infiltrates. Also, a general score will be calculated to identify normality vs abnormality indicating the needy of medical attention.

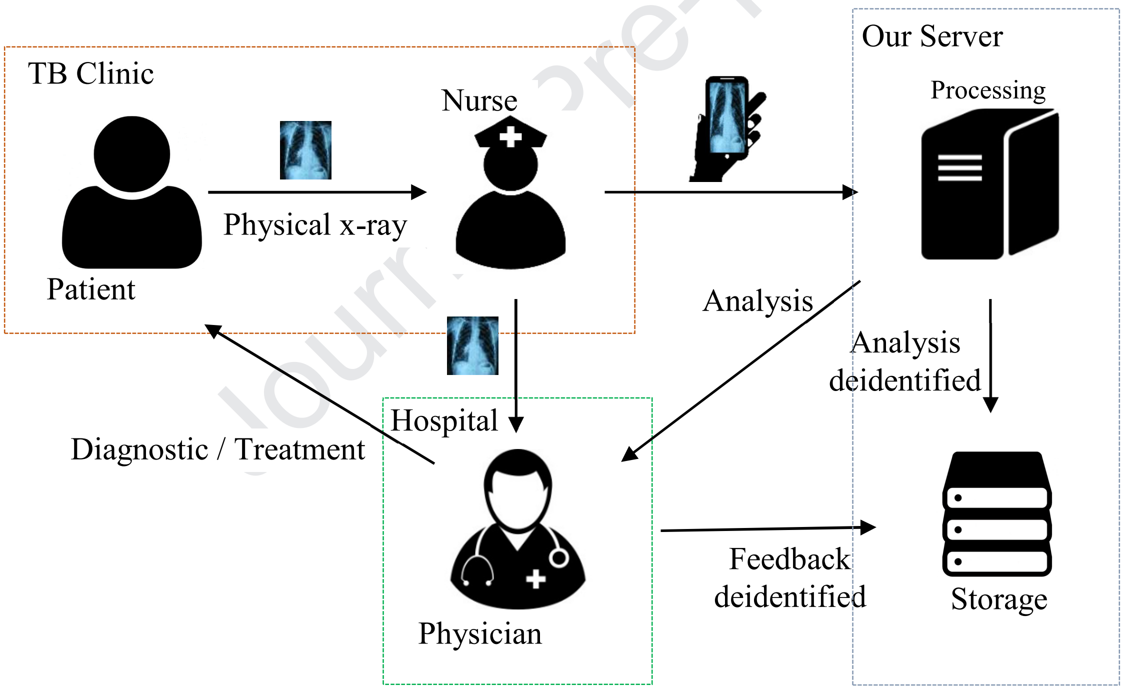

Figure 4: Flowchart illustrating the communication between the professionals and the server

4.3. Physician Feedback and Diagnostic

The current online tool for analysis is available at *erx.southcentralus.clouapp.azure.com*. The eRx system for X-ray analysis is intended only for physicians and pulmonologists. Other healthcare professionals use the eRx app, a mobile tool to register a patient and upload pictures of the X-ray.

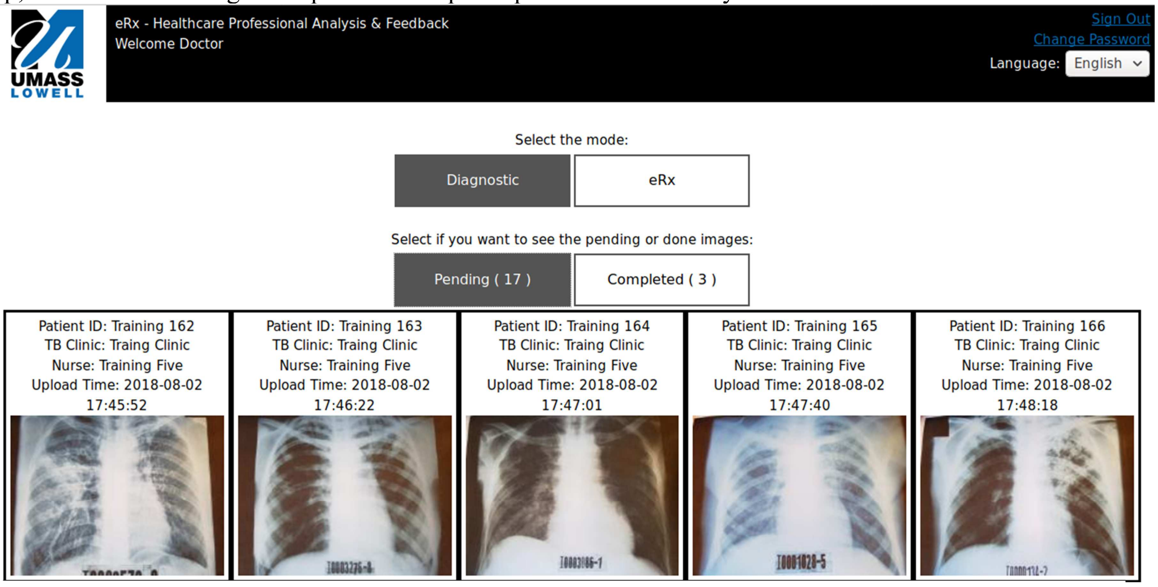

Figure 5 – eRx selection page

Figure 5 shows the X-ray selection page where the physician can pick one X-ray to analyse, the page shows the patient ID, the nurse responsible for the upload and the TB clinic the patient visited. The physician will then choose to provide his own analysis or check the automatic analysis done by eRx. The automatic analysis becomes available only after the physician provides his own diagnostic.

Figure 6 shows the diagnostic page where the physician may entry the professional diagnostic without any assistance from eRx, the diagnostic in this case is based in the X-ray and supported documentation uploaded by the nurse, this diagnostic is stored and cannot be changed after the physician reads the automatic analysis. Besides the diagnostic some general feedback is asked, about the overall quality of the images and a general feedback about the process.

In the Figure 7 we can see the page where the physician is able to provide the feedback about the automatic analysis. The diagnostic obtained through the machine learning algorithms is finally shown and we then ask if the physician according to his/her own experience, agrees with the diagnostic. The physician may justify his/her answer and send the feedback. Please note that the feedback of each image will be obtained by at least 3 distinct physicians, therefore we can compare the feedback in a further step.

5. Discussion

5.1. Healthcare in LMICs

As explained, TB is an illness that has medical treatment and can be partially preventable by vaccine. Although, it is a problem for LMIC countries mainly due the lack healthcare resources in the poorer communities.

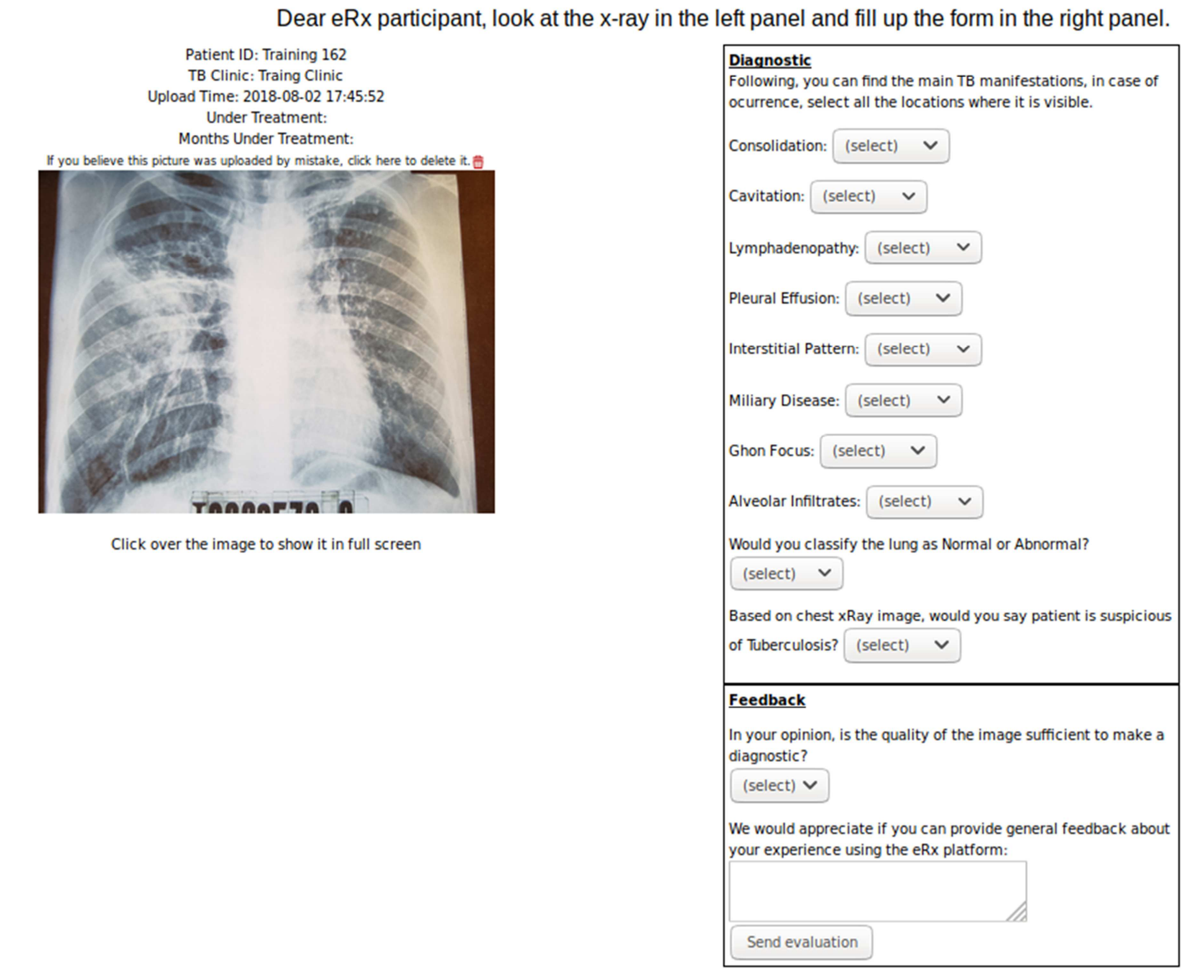

Figure 6 – eRx diagnostic page

TB requires medical diagnosis with lab tests or imaging exams. It is a problem in LMICs countries that the exams are not always assessible for the poorest people and even after getting them, it is hard to find a doctor available in the clinics. Patients may die or spread the illness in the meanwhile aggravating the situation.

When there is no health infrastructure, some informal practices are common, like diagnostics provided by nurses, pictures or reports of patients send over the Internet with no security, or X-rays being analyzed by non-specialized practitioners.

With an optimistic workflow, a patient may wait for more than 2 weeks to get his medical record analyzed and even more to have an appointment with a physician. A mobile technology and automatic diagnosis system can help in this precarious scenario by providing to the nurses a way to identify the more urgent cases to forward them directly to the pulmonologist.

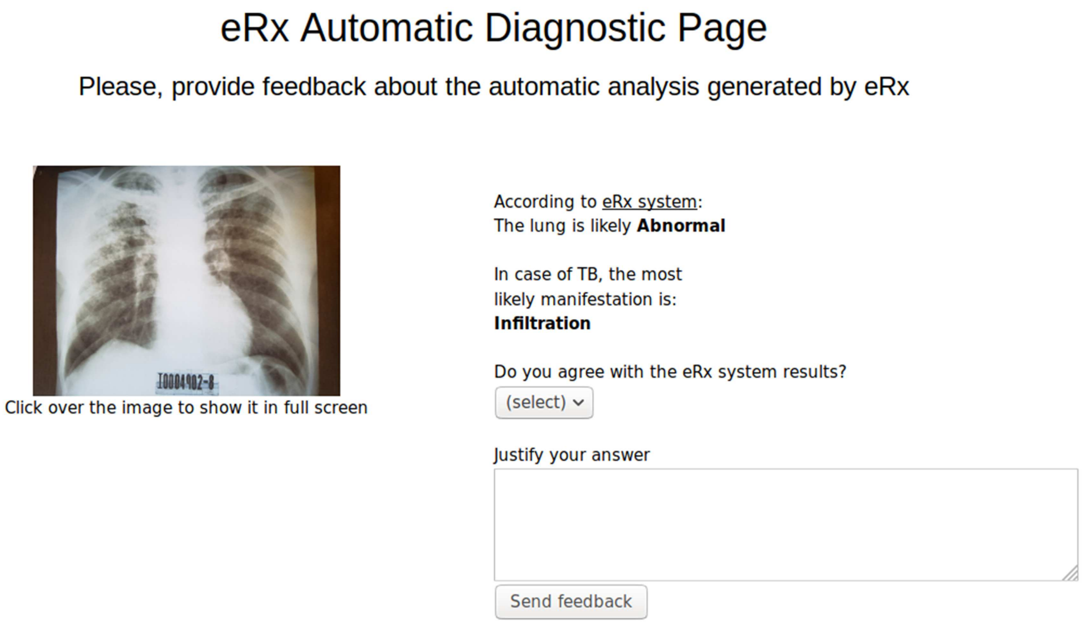

Figure 7 – eRx automatic diagnostic page

5.2. Mobile technologies on Health (mHealth)

Even in developing countries, the use of mobile technologies is very popular, almost everyone has a smartphone, even in the poor population. Among the health care professionals, the use of technology is still more predominant. To include mobile systems to help aiding the TB diagnostic seems feasible in this first analysis, once the hard processing of everything is done in powerful services, the mobile phone being only a terminal to send the data to the platform, making the implementation of the system, technologically cheap.

However, the use of mobile technologies in the health care system involves other costs, like training of the professionals and the maintenance of the technology that must be updated once feedback is obtained. Use of mobile technologies in healthcare is possible when there is a close collaboration between the technical team and the healthcare professionals, and a raise in the awareness among the population.

5.3. Computer Aided Diagnosis

The computer aided diagnosis is already a reality, in some areas the software performs a diagnostic more reliable than the one provided by the physician, however it is not a competition and we do believe that the best solution is the collaboration between medical and computer area, when physicians can interact with digital systems we can obtain the best of both solutions. It is important to notice that technology may never fully replace all the aspects of a physician, as treatment may consider other aspects of community and the patient's life.

However, some patterns in patients' images may be not visible for human eyes, the chain of events that may trigger an illness is not always clear. The physician diagnostic enriched by computer analysis may lead the diagnostic process to a better level and can make the work for physicians easier and reduce the waiting times for patients.

The bureaucracy in the health systems also play against a faster diagnostic. In weak healthcare systems there are still more common cases of missing exams, or matching the wrong medical record, duplicate medical records, and other serious problem due the susceptibility of humans to fail sometimes. In computer systems the errors are not very common and when they happen, they can be tracked and usually corrected in time.

5.4. eRx Development

eRx as a tool to physicians is in an early stage of development, most likely many of the features will change according with the feedback from the healthcare professionals, as well as we acquire more knowledge of how a computer program can provide or enhance a diagnostic that can be interpreted in a real case scenario.

6. Conclusions

According to the World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC), tuberculosis remains one of the world's deadliest diseases. Most of the infected populations are from resource-poor communities with weak healthcare infrastructure and lack of human resources. For this targeted population, mobile technologies have the potential to reduce the burden of TB to the clinics by providing mobile computing and communication techniques, as well artificial intelligent systems to aid the diagnostic, treatment and prevention in these communities. The goal of our research is to reduce patient waiting times to be diagnosed with TB by implementing a socio-technical solution to optimize the diagnosis process. As the first step of this research project, in this paper, we introduced the two major progresses we have made. The first progress is to build a large-scale, real-world, and well-annotated chest X-ray image database dedicated for TB screening. The second progress is to develop effective and efficient computational model for TB manifestation categorization. Preliminary results have demonstrated the feasibility of the proposed approach.

Based on the proposed framework and the preliminary work reported in this paper, our final goal is to produce a scalable solution to improve healthcare system in Peru, and globally with mobile technologies. We will continue to develop the large scale, real-world X-ray TB database with reliable content annotated by a trained team and verified by a specialized pulmonologist, as well as continuing to improve the performance of the computing algorithms in identify TB manifestations. As future work we will implement a scalable solution by making the mobile device-based computer-aided system available as an open source software platform. The project's next step now is a field testing evaluation at TB clinics in the districts of Carabayllo, Comas and

Independencia in Lima, Peru, which was already accepted for the Institutional Review Board in Peru where the study will be made and the Institutional Review Board in the United States where the research and data analysis is being performed.

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