Artificial Intelligence for Opportunistic Chest CT Screening and Prognostication

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Published in:
Artificial Intelligence in Cardiothoracic Imaging

DOI:
10.1007/978-3-030-92087-6_45

Publication date:
2022

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Introduction

Low-dose chest computed tomography (CT) can help detect cancer in early stages and has been found to significantly improve the survival of long-term smokers [1, 2]. Trials have shown that low-dose CT screening prevented death due to lung cancer in up to 25% of cases [1, 2]. Since the publication of these large-scale trials, there has been increasing interest in implementation of lung cancer screening in healthcare practice. This has resulted in recommendations from major societies particularly in the USA [3], on the criteria for individuals who are recommended to undergo chest CT screening, aimed at early lung cancer detection. In Europe, there is still more hesitation with regard to CT screening implementation, as a number of questions still need answering (ESR/ERS and EUPS statements [4, 5]).

Apart from early detection of lung cancer based on lung nodules, chest CT scans can also help in the early detection of emphysema, as a marker for chronic obstructive pulmonary disease (COPD). Presence of emphysema on CT has been found to be a predictor of mortality [6] and of lung cancer [7] in screening setting. Visual and quantitative evaluation of emphysema may provide complimentary information related to prognosis [8]. Moreover, chest CT can provide useful information on the presence and severity of coronary artery calcium (CAC), which is related to the risk of cardiovascular disease (CVD) [9]. While the standard method for evaluating the CAC score, as quantification of CAC, is an electrocardiographically triggered cardiac CT scan, lung cancer screening studies have shown that a CAC estimate based on low-dose chest CT is also related to risk of CVD events [9].

For COPD and cardiovascular disease screening, results from randomized trials showing benefit of early detection, combined with early treatment, are lacking. The ROBINSCA trial aims to determine the benefit of CAC screening based on non-contrast cardiac CT [10]. For the foreseeable future, it is likely that if chest CT screening is indeed implemented in Europe, it will be aimed at long-term (ex-) smokers, and focused on early detection of lung cancer. This screening population would comprise a huge number of screenees, undergoing potential (bi-)annual CT screening. If eventually CAC screening would be implemented, the population that would qualify for that screening would likely be much larger than for lung cancer screening, as risk factors are much broader than smoking alone and include hypertension, diabetes, and hypercholesterolemia, factors that are highly prevalent in the Western populations.

The challenges associated with CT screening of a large population group are numerous. These include logistics (invitations, administration of baseline and follow-up screenings), capacity of CT systems, standardization of CT protocols, image quality and evaluation protocols, and manpower to evaluate the CT scans [5]. All these issues contribute to screening costs. The screening workload can put a huge burden on radiologists' time to evaluate, register, and check the results of the scans [11]. This will result in fatigue, which in turn will decrease radiologist's performance of detecting nodules and reading speed [12]. In addition, the scans of many of the individuals that will be screened will be without abnormalities, with a negative screening result. The question is whether image reading can be optimized with better selection of scans that need radiologist evaluation.

AI can help to address, among others, the abovementioned issues. It can automatically detect small lung nodules by finding complex patterns or even detect features that would otherwise be missed, reducing the time radiologists need to spend on reading CT scans, and so, reducing the total

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C. N. De Cecco et al. (eds.), *Artificial Intelligence in Cardiothoracic Imaging*, Contemporary Medical Imaging,
https://doi.org/10.1007/978-3-030-92087-6_45

cost of screening [13]. Moreover, it can prioritize the workflow by moving screenees with significant findings to the top of the list of scans that the radiologist will assess. In addition, it can save time by automatically quantifying the size of nodules found. Furthermore, AI seems promising in reducing noise in reconstructed images, and so the dose required during the scan can be further reduced and the acquisition time can be decreased [14, 15]. These topics are further explored in the remainder of this chapter.

Another difficulty in clinical practice is to evaluate all relevant biomarkers related to B3 diseases. The National Institutes of Health Biomarkers Definitions Working Group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [16]. A biomarker should provide information about disease risk to a greater extent than the standard risk factors like age, smoking, etc. [17]. A challenge in implementing biomarkers is the fact that different CT systems, scan protocols, reconstructions, and software may yield differences in biomarker results [18]. Thus, standardization, for example, in image quality, is needed. Also, the value of a biomarker in relation to clinical disease and events needs to be determined for different populations in order to understand generalizability. Also, we should take into account the inherent correlation between biomarkers, and perform validation to make certain that the biomarker is reproducible and accurate [17].

Machine learning methods have started to allow automatic extraction of useful features from images like nodule size, diameter, shape, etc., which help to derive new imaging biomarkers, some beyond the visual and (semi-)quantitative analysis by a radiologist. Before the rise of these methods, this task was usually performed manually, by experienced radiologists who used to spend a significant amount of time to find and extract these features. It is worth noticing that a biomarker will be more useful in clinical practice if it is more informative than just the imaging alone [19].

Finally, if biomarkers will be used to predict the outcome of a disease in a screenee, there are some indicators of how well they perform compared to other available biomarkers. These are their discrimination ability and their calibration and reclassification by evaluating statistical models with and without the biomarker [17].

Potential for AI Role in B3 Screening

There are many ways in which AI can help in the workflow of B3 screening (either aimed at lung cancer, emphysema, CVD, or all three). Figure 45.1 shows the different steps where AI may have value in the future.

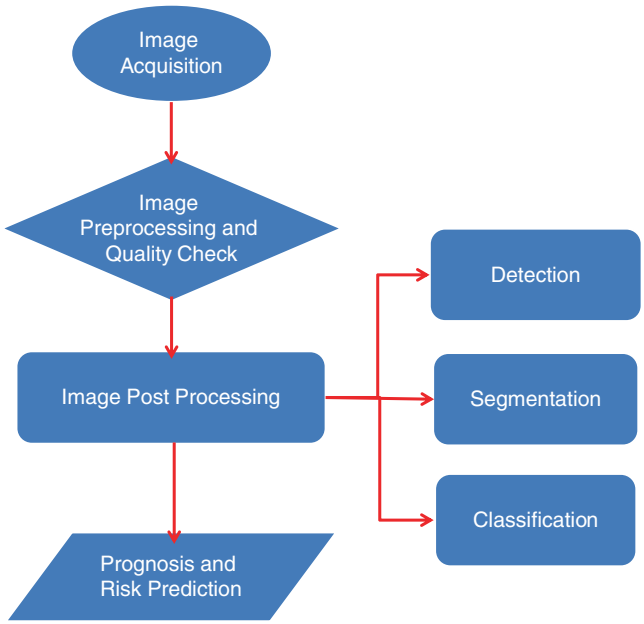

Fig. 45.1 Workflow steps in B3 screening which AI can contribute

Image Acquisition

The first step in the pipeline of low-dose chest CT screening is the image acquisition. Recently a system based on deep learning was developed that uses 3D cameras to find the optimal position in which an individual should be positioned for the CT scan. By doing that, the right amount of dose will be delivered to the right location, and the image quality can also be improved and homogenized, since noise in the output image will be reduced [20].

Image Pre-Processing

The next step in the pipeline is the pre-processing of the acquired CT images into a standard format (normalization, resizing, etc.) and to check if they have an adequate quality to perform diagnosis [21]. In this step noise reduction techniques are applied, in particular iterative reconstruction. AI can also be used instead of classic iterative reconstruction procedures, to improve image quality of low-dose CT scans by reducing noise and improving structural fidelity [22]. Image improvement algorithms which reduce noise and artifacts (Fig. 45.2) are of importance since radiation dose can be reduced, due to the fact that the decreased image quality can be compensated by the noise reduction algorithm. There may even be the possibility in the future to generate contrast-enhanced CT images out of non-enhanced ones [23]. Also, images from different CT scanner vendors can be made more alike in quality, by using vendor-neutral deep learning image reconstruction software [24].

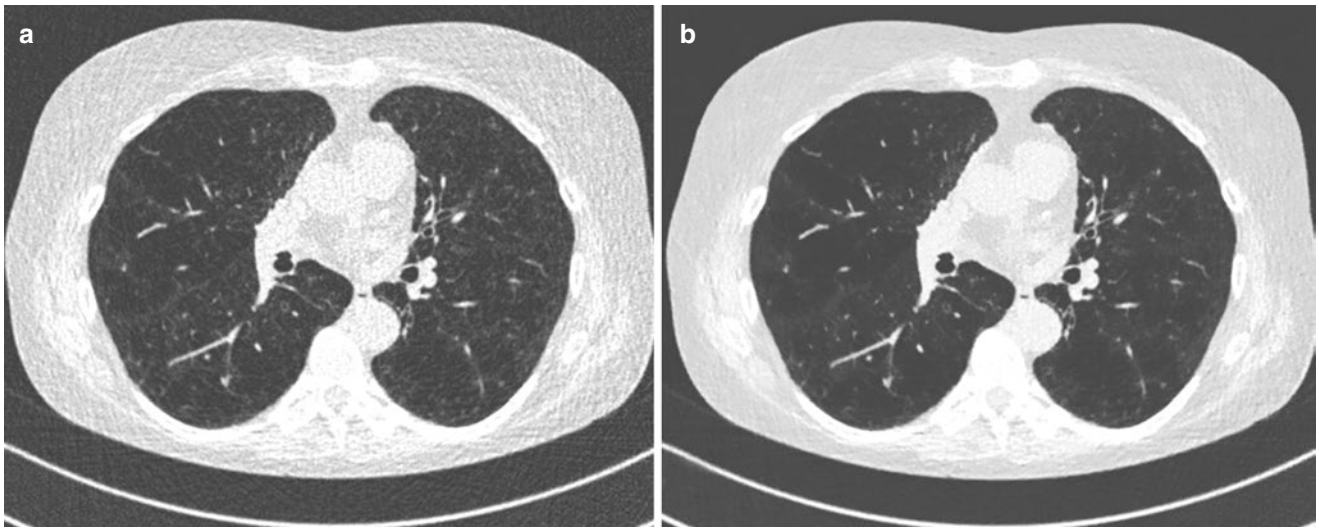

Fig. 45.2 AI for noise reduction. On the left (**a**) the regular chest CT image and on the right (**b**) the improved, reduced-noise version, generated by the AI algorithm [13]

Image Post-Processing

The next step is the post-processing. Here, the preprocessed images are fed to an AI algorithm which either detects the region of interest or segments the lesion or classifies the image according to the goals. After that, the scan result for the particular screenee is determined. Using the results from image post-processing, a risk prediction algorithm is then used to determine the risk of the screenee. The prognosis is estimated, and at the end, it is decided if another routine screening needs to be scheduled or if workup or short-term follow-up is required.

Below, a few specific applications of AI in image post-processing of B3 diseases are presented:

1. Object detection: Object detection algorithms identify specific objects in an image by drawing a bounding box around them. Examples of these algorithms are the R-CNN, the fast R-CNN, the faster R-CNN, and the mask R-CNN [25]. An application of such algorithms could be to find a region of interest in an image (Fig. 45.3). Lung nodules can also be detected using CNNs. An example of lung nodule detection can be seen in Fig. 45.4. Using maximum intensity projection CT images, the number of false positives per scan can be reduced significantly [26]. Except from the higher sensitivity, a recent study has shown that an AI system can have better performance compared to radiologists in the lung nodule detection task [27]. Based on the findings and on risk factors [28], the AI will then decide if additional screening is needed.
2. Segmentation: Segmentation is a per-pixel classification task. A label is given to each pixel as belonging to one of a set of predefined categories, and at the end, a mask is applied to segment the region of the image that contains the pixels of a specific category [30, 31]. An example of a segmentation algorithm is the U-net which can be used to segment coronary artery calcium, a predictor of cardiovascular events [30]. The Dice coefficient can be used to evaluate the results of the segmentation to the ground truth (e.g., manual segmentation) [30]. In Fig. 45.5 a segmentation of the heart is presented.
3. Classification: Classification algorithms classify patients to one of a set of predefined categories (e.g., patients with

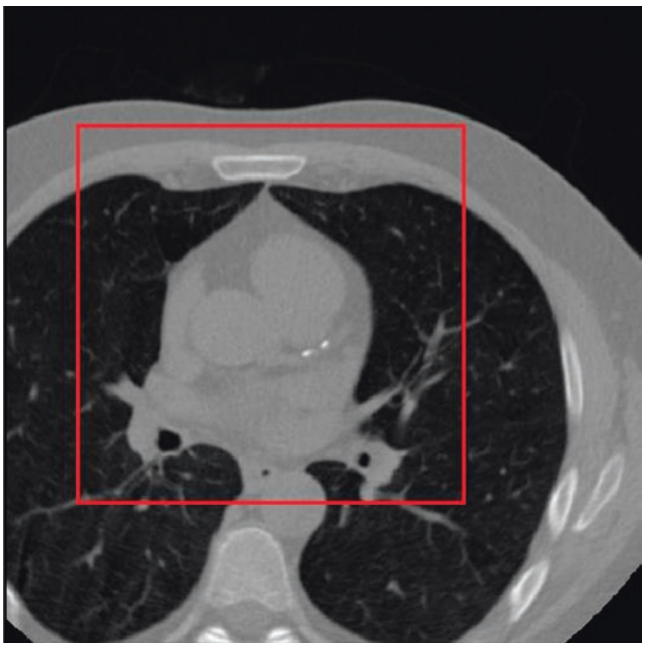

Fig. 45.3 Object detection algorithm outputs a bounding box around the heart [13]

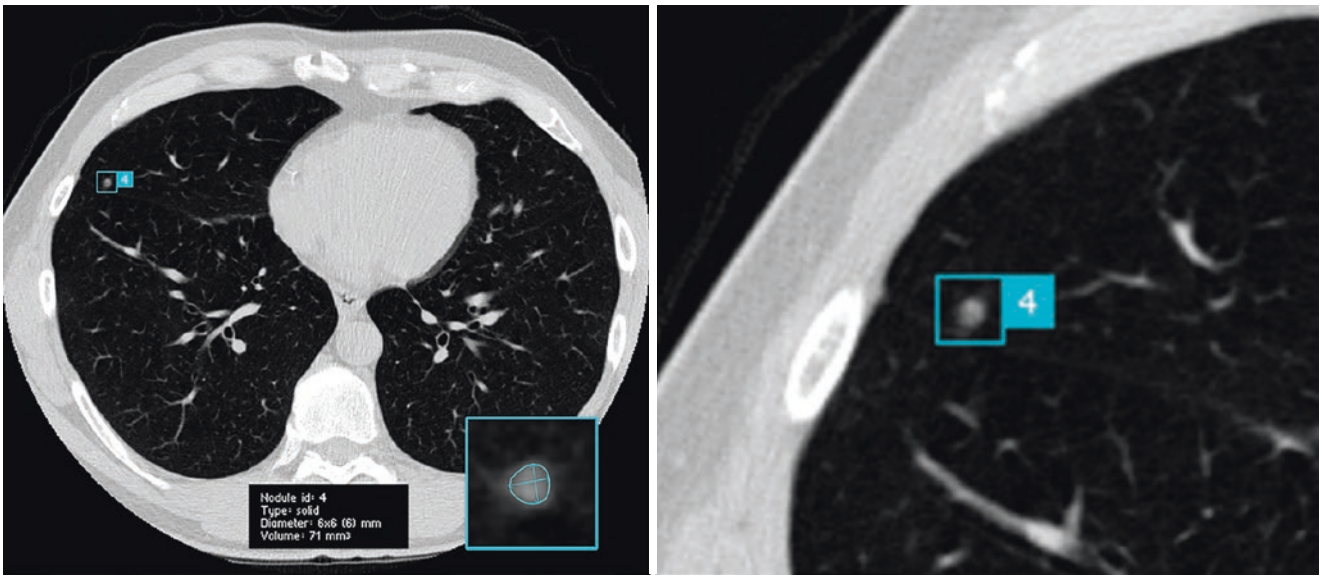

Fig. 45.4 Bounding box around a lung nodule on chest CT, with a magnified view on the right [29]

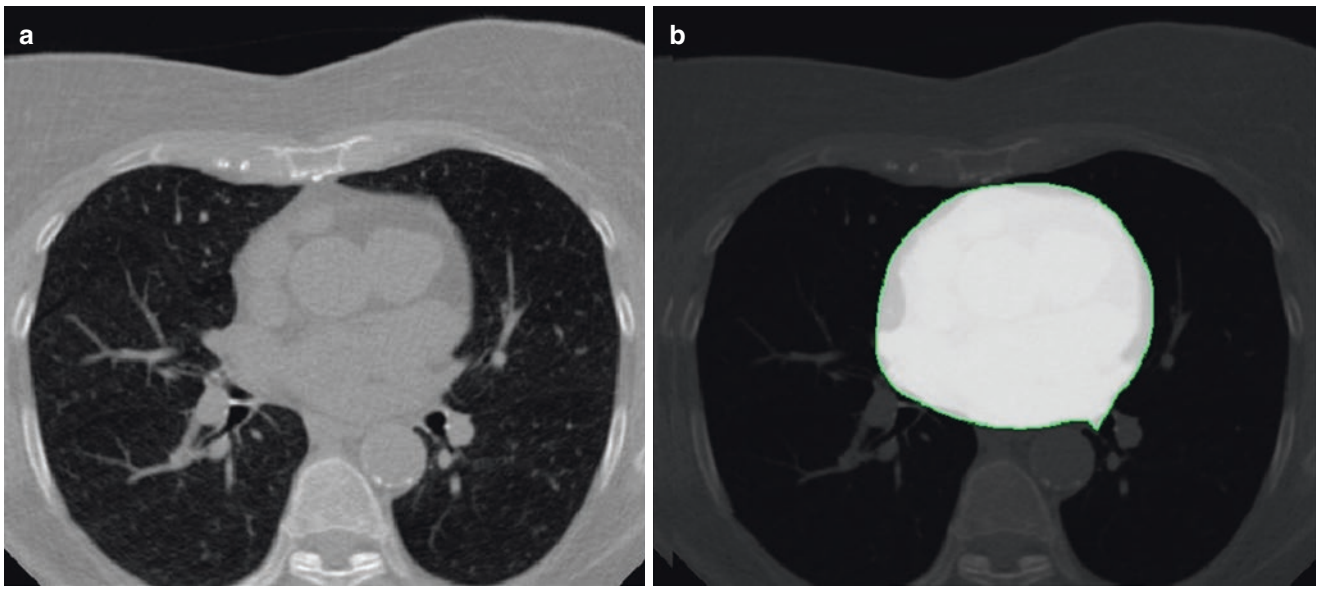

Fig. 45.5 Segmentation of the heart. On the left (**a**) the input image and on the right (**b**) the binary segmented image projected over the original CT image [13]

or without myocardial infarction). A deep neural network (DNN) can be used to directly classify lung nodules in an image as benign or malignant. Nodule features can be extracted from these networks and fed into a machine learning classifier.

Next, another algorithm can be used to further improve the performance of the model [32]. The whole process is demonstrated in Fig. 45.6.

Prognosis and Risk Prediction

Prognosis and risk prediction algorithms based on AI have recently become available. These algorithms output a continuous function with a numerical output indicating, e.g., the cardiovascular disease risk and/or the survival time of patients [33]. Inputs can also be biomarkers instead of images. For assessing the risk of individuals, methods like the Framingham risk score (FRS) and body mass index

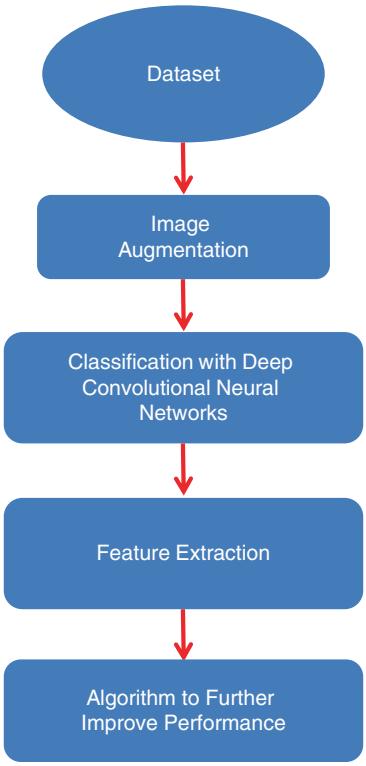

Fig. 45.6 To classify chest CT images with deep learning models, augmentation is often used to increase the examples in the training set; features are extracted after the model is trained. These features are used as input to another algorithm to further improve the performance of the deep learning network

(BMI) for CVD are commonly used. These methods consider a number of biomarkers like cholesterol levels to evaluate the risk score [34, 35]. A recent study showed that automated CT-based biomarkers derived from image processing algorithms are more accurate in predicting cardiovascular events compared to FRS and BMI [36]. Moreover, one other study revealed the potential of using AI methods to uncover new predictive factors in CVD [37]. For lung cancer, the risk can be estimated from an AI algorithm including lung nodule volume [38].

It is worth noting that there are also some cluster analysis algorithms that help us find patterns in data without any prior knowledge about the patterns that exist in the data. An example of these algorithms is hierarchical clustering that is used for heterogenous cardiac diseases; these algorithms could help us understand the mechanisms that cause heart failure [39].

Clinical Implementation

AI has revolutionized the medical field. Nevertheless, there are many challenges to applying AI algorithms in clinical practice. Below the most important ones are presented.

Technical Considerations

The mechanisms that lead most of the AI algorithms to their predictions are not well understood. This is the so-called "black box" problem with AI systems, which means that the processes and calculations that take place may not be easily interpreted by humans. The algorithms lack explainability, and so their predictions cannot be treated without suspicion by the clinicians [40, 41]. For detection objectives, one possible solution to address the lack of explainability is to use Grad-CAM method. In that method the areas in the output image that influenced the output of the algorithm the most are visualized [42]. Furthermore, by having more GPU memory, it is possible to train 3D CNNs which will be able to better detect the regions of interest in images (e.g., nodules) [31].

Population Characteristics

The deep learning training process is highly dependent on the input data and the corresponding labels in that the deep learning network can only learn from examples provided to it. Therefore, imbalance in these input data might influence the decision-making capacity of the deep learning network or make it less generalizable. The influence of imbalance on the deep learning network could, for example, lead to discrimination of certain minority groups in the training data either causing bad performance in certain groups or resulting in misclassification. The decrease in generalizability can lead to decreased performance of a deep learning network when deployed in another environment. For example, one study showed that there is a significant difference in cardiometabolic biomarkers between women and men [43]. It is therefore possible that these differences between biomarkers in women and men will lead to variations in development and complications of CVD and, so, in potential gender-specific early misdiagnosis [44]. If this is the case, we would have bias even if the dataset is balanced in terms of the population of each sex. Another example could be the presence of a specialized doctor for a particular type of rare lung cancer in a hospital. This will lead patients from all around the country to this hospital to be examined by this specialist. Since this is a rare cancer, it is likely that patients who do not live close to the hospital are having this type of cancer, while those who live near that area are not having it. It seems like there is an inverse correlation between distance to the hospital and having the rare cancer, even though these two variables are independent [45]. So, living in a country in which a specialized doctor is only available in one hospital from which data were collected and used to train an AI algorithm could make the algorithm learn wrong patterns. This can

only be avoided by adding data from other hospitals and from different countries as well, since in those data it is likely that this correlation does not exist and, so, it would be possible to make the algorithm generalize better.

Dataset Challenges

Acquisition characteristics should be taken into account during dataset creation. If the dataset consists of images from multiple CT systems, it may be the case that they do not have the same characteristics. The resolution, the slice thickness, the reconstruction kernel, etc. may differ between images of different datasets, and so their quality will not be the same [46]. This can severely impact the performance of our AI algorithm since, for example, it may only be able to localize small nodules in high-resolution images.

In addition to that, many medical experts should take part in the annotation procedure of the dataset to ensure that it is done properly [47]. This will inevitably introduce interobserver variability which should be resolved [47]. Lastly, it is essential to preprocess the images that are fed to the model to ensure that they are in the format that the AI algorithm was trained on [39]. Otherwise, wrong results will be obtained.

Application Area

During training of an AI algorithm, the dataset should be representative of the type of data and of the population that the algorithm will see in the future [47]. If, for example, the goal is to detect skin cancer in the general population, the dataset should consist of people of all colors, so that minorities are also included, to prevent selection bias. In addition to that, specific medical requirements should be taken into account. For example, it may be more important to have less false positives even at the cost of increased false negatives and vice versa. It is also very important to notice that an AI algorithm is likely to be trained with more images of patients than of healthy individuals and, so, be biased in favor of diagnosing disease instead of healthiness. In screening, it is not known in advance if someone is healthy or not. It is likely that the individual is healthy since screening is mainly performed on asymptomatic individuals. Therefore, AI software may fail to work in screening because of that class imbalance. It would be better to train AI algorithms with equal amounts of data from each class (here diseases and healthy individuals). One way to test the performance of the algorithm in class imbalance problems is to train it with different splits of images between healthy and diseased. For example, a training set may consist of 40% diseased and 60% healthy individuals or 30% and 70% or any other split. It should be noted that there may be a decrease in accuracy if bias is reduced, considering that having less training data of diseased may not allow the algorithm to achieve the detection performance that would have if the training set consisted of equal amounts of images of diseased and of healthy individuals. Another way to deal with the decreased performance is to use techniques like oversampling of the minority class, in which more copies of the minority class are added in the training set, or undersampling of the majority class, in which some of the data of the majority class are removed, or, similar to upsampling, generate new examples of the minority class [48]. Moreover, data augmentation could be an option for the examples of the minority class.

Legal Challenges

Another limitation that may prevent the use of AI in clinical practice is the massive datasets required to train a model, which are difficult to be acquired, especially when they contain sensitive screenee information. It is important to respect privacy regulations and secure the anonymity of the individuals [47]. Another legal aspect could be the accepted role of AI in a screening setting. AI could play a major role in the cost-effectiveness of large population screening programs if it could safely discriminate between participants who do not have disease and participants who are suspected of having disease with a varying likelihood. The legal issue however would be if an AI system, although capable of doing so with very high accuracy, could be allowed to discard screening participants from further investigation without any human intervention. The question is whether a human expert check would still be required, also for those participants of which the algorithm is 100% sure they do not have any of the diseases screened for. Since most AI nowadays are aimed at a single defined task, it could, for example, be argued that a screening AI that safely rules out lung nodules, COPD, and coronary calcification could miss something a human observer would be able to detect (e.g., thoracic aorta aneurysm). Having AI systems trained and implemented for all possible pathologies that could show up in screening would be very challenging and increase the cost dramatically.

AI Benchmarking

To avoid many of the above problems, validation of software based on a benchmark dataset should be performed. This dataset should be created trying to avoid as many biases as possible. The characteristics of the population data that were collected along with the characteristics of the CT systems used to acquire the data can significantly affect the performance of the AI algorithm. Therefore, standardization/normalization of the data should be performed. Moreover, it

should be ensured that the dataset is representative in terms of resolution of images, slice thickness, etc. of the data that will be given as input to the AI algorithm in the clinical practice. Additionally, this dataset should be tailored to a specific area of application (e.g., lung nodule detection) and to a specific target population (e.g., white individuals of ages 30–40). Moreover, harmonization of annotated data from different studies should be performed since each study may have a unique annotation protocol. Furthermore, batch effects and human observer difference may arise because of the different times the annotations were performed and of the different radiologists that contributed in the annotation tasks, respectively. Statistical tests can help check the coherence of these data as well as test their variation. Only if all the above suggestions are followed, the generalization of the algorithm as well as its broad coverage can be tested. At the end, there may still be some inherent biases that cannot be avoided.

Conclusion

Even though AI's potential in assisting medical experts in B3 screening, prediction, diagnosis, and many other tasks is promising, with specific tasks having proven benefit in many studies, a lot of work needs to be done before AI algorithms can be implemented in chest CT screening. It is important to ensure that most of the potential biases are avoided, that the algorithm can be generalized to the scan protocol, and that the dataset it was trained on resembles the target population. AI algorithm validation is an essential step before allowing algorithms to be used in medical practice.

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