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Review Article

Artificial intelligence for early diagnosis of lung cancer through incidental nodule detection in low- and middle-income countries-acceleration during the COVID-19 pandemic but here to stay

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Abstract: Although the coronavirus disease of 2019 (COVID-19) pandemic had profound pernicious effects, it revealed deficiencies in health systems, particularly among low- and middle-income countries (LMICs). With increasing uncertainty in healthcare, existing unmet needs such as poor outcomes of lung cancer (LC) patients in LMICs, mainly due to late stages at diagnosis, have been challenging-necessitating a shift in focus for judicious health resource utilization. Leveraging artificial intelligence (AI) for screening large volumes of pulmonary images performed for noncancerous reasons, such as health checks, immigration, tuberculosis screening, or other lung conditions, including but not limited to COVID-19, can facilitate easy and early identification of incidental pulmonary nodules (IPNs), which otherwise could have been missed. AI can review every chest X-ray or computed tomography scan through a trained pair of eyes, thus strengthening the infrastructure and enhancing capabilities of manpower for interpreting images in LMICs for streamlining accurate and early identification of IPNs. AI can be a catalyst for driving LC screening with enhanced efficiency, particularly in primary care settings, for timely referral and adequate management of coincidental IPN. AI can facilitate shift in the stage of LC diagnosis for improving survival, thus fostering optimal health-resource utilization and sustainable healthcare systems resilient to crisis. This article highlights the challenges for organized LC screening in LMICs and describes unique opportunities for leveraging AI. We present pilot initiatives from Asia, Latin America, and Russia illustrating AI-supported IPN identification from routine imaging to facilitate early diagnosis of LC at a potentially curable stage.

Keywords: Artificial intelligence, incidental pulmonary nodules, low- and middle-income countries, lung cancer, screening

Introduction

Lung cancer (LC) is the leading cause of cancer-related mortality globally, accounting for 11.4% of all incident cancers and 18.0% of all cancer deaths in 2020 [1, Global Cancer Observatory 2020, https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf]. With a steady burden of risk factors, LC mortality is projected to reach 2.45 million annual deaths worldwide by 2030 [https://www.chestnet.org/News/CHEST-News/2020/07/World-Lung-Cancer-Day-2020-Fact-Sheet]. Identifying LC at an early stage allows for potentially curative treatment, thereby improving survival. Early diagnosis in the asymptomatic stage through intentional screening programs or incidental radiographic pulmonary nodule identification and follow-up, significantly improves outcomes. However, there are large gaps in the screening and early detection of LC, especially in low- and middle-income countries (LMICs)-driven by socioeconomic, genetic and infrastructural risk factors, alongside scarcity of specialized human resources and technological capacity [2-5].

We describe opportunities for early LC diagnosis through artificial intelligence (AI)-assisted incidental pulmonary nodule (IPN) detection from other noncancerous imaging, such as the current coronavirus disease of 2019 (COVID-19) pandemic, with special focus on LMICs. We also present case studies from LMICs illustrating the strategic process of AI-supported IPN identification from routine imaging to facilitate early diagnosis, when LC is at a potentially curable stage.

Importance of lung cancer screening

Globally, both developed and developing countries have a high burden of LC (**Table 2**). Early LC is largely asymptomatic until the advanced stages, with 50%-75% of LC being diagnosed at stage IV [6, cancer.ca/Canadian-Cancer-Statistics-2020-EN]. The 3-year survival for LC at stage IV is only 5%, but can rise to 71% if diagnosed early at stage I [cancer.ca/Canadian-Cancer-Statistics-2020-EN]. Empirical evidence has revealed that the proportion of patients diagnosed at an advanced stage in LMICs is higher, with an even sharper drop in the 5-year survival rates [1, National Cancer Institute, Five-Year Survival Rates, SEER Training https://training.seer.cancer.gov/lung/intro/survival.html] (**Table 3**) [6-13, Azizah AB. Malaysian National Cancer Registry Report 2007-2011. https://www.crc.gov.my/wp-content/uploads/documents/report/MNCRR-repor2007-2011.pdf]. LC detection is difficult in the presence of coexisting respiratory diseases such as chronic obstructive pulmonary disease (COPD), and as the initial nonspecific symptoms are often ignored by patients, diagnosis and treatment might be delayed [8, 14-16].

This necessitates adequate measures for diagnosing LC early in the asymptomatic stage. Detecting LC at an early stage (I to IIIA) potentially allows for surgical resection ± (neo) adjuvant therapies, which gives the greatest chance of cure. Novel therapies including targeted and immune-oncology therapies are being intensely studied in early-stage LC and could further improve patient outcomes [17-19].

Multiple randomized trials, including the recent NELSON trial, have provided definitive evidence that low-dose computed tomography (LDCT) screening of at-risk individuals can reduce LC mortality [20-22]. Based on traditional evidence, the United States Preventive Services Task Force (USPSTF) recommended annual screening for LC with LDCT [https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/lung-cancer-screening1]. However, recently the USPSTF concluded that annual screening for LC with LDCT has a moderate net benefit among high-risk individuals, depending on limiting screening of high-risk individuals, accuracy of image interpretation, and resolution of false-positive results with serial imaging [23].

Current landscape and challenges of LC screening in LMICs

Despite the evidence on benefits of LDCT screening for LC, the implementation of nationwide programs in developed countries is in a nascent stage [24-26]. In the U.S., uptake of annual lung screening among eligible people was low (12.5%)-before the USPSTF LC screening recommendations broadened the target population further [27]. Developing countries are exploring avenues through pilot programs to evaluate the feasibility of conducting population-based LDCT LC screening; however, challenges including gaps in capacity hinder implementation [28, 29] (**Table 1**). In Mexico, although a national screening government initiative was announced in 2018, economic uncertainty prohibited the actual implementation [30]. Similarly, low participation rates and high missed cases for LC diagnosis were reported from China [31]. Low rates of LC screening despite clear recommendations highlight the need for pragmatic region-specific strategies in LMICs.

Access to screening radiology and medical expertise

Access to imaging including computed tomography (CT) scans and the radiology expertise for accurate interpretation is limited in LMICs-prevents program implementation through models adapted from affluent countries [19, https://data.oecd.org/healtheqt/computed-tomography-ct-scanners.htm]. Alongside barriers of economic cost and limited access of CT scans for clinical care management in LMICs, probability of screening asymptomatic patients in a preventative setting would be very low [32, 33].

Table 1. Different barriers and challenges for organized lung cancer screening in low- and middle-income countries

	Barriers	Potential solutions
Patient-related	Limited access to screening radiology	● Building infrastructure such as community centers/mobile units for equitable outreach ● Telehealth
	Lack of patient awareness with fear of cancer diagnosis and poor adherence to recommendations	● Provider-support through integrated multidisciplinary management ● Discussions with patients regarding benefits and harms
	Economic and financial constraints	● Expansion of insurance coverage ● Utilization of routinely available chest X-rays and CT scans for detection of IPN
Physician/health system-related	Identifying the population at risk, especially when smoking is not the predominant etiology, such as multiple biological and environmental etiological factors	● Digitization and use of health records to help identify high-risk individuals ● IPN detection in routinely available chest X-rays and CT scans
	Lack of medical expertise/trained human resources leading to false-positives or over-diagnosis	● Optimized provider education program with specific guidelines and protocols ● Clinical decision support by utilization of digital health technologies like AI
	Prevalence of other pulmonary diseases affecting diagnostic accuracy	● Utilization of digital health technologies to aid diagnosis
	Fragmented healthcare with lack of national/integrated databases or referral systems hinder identification of high-risk patients, leading to gaps in screening and timely referral	● Creation/expansion/digitization of national cancer databases/registries ● Creating multidisciplinary teams ● Fostering public-private partnerships
	Impact of COVID-19 pandemic	● IPN detection in routinely available chest X-rays and CT scans by digital health technologies such as AI

AI: artificial intelligence; CT: computed tomography; COVID-19: coronavirus disease of 2019; IPN: incidental pulmonary nodule; LMICs: low and middle-income countries.

Table 2. Burden of lung cancer in developed and developing countries (2020)

		Proportion of region-specific incidence	Proportion of region-specific 5-year prevalence	Proportion of region-specific mortality
		Total (N) = 2,206,771	Total (N) = 2,604,791	Total mortality (N) = 1,796,144
		n (%)	n (%)	n (%)
Developed countries	North America	253,537 (11.5)	328,224 (12.6)	159,641 (8.9)
	Europe	477,534 (21.6)	582,924 (22.4)	384,176 (21.4)
Developing countries	Asia	1,315,136 (59.6)	1,515,321 (58.2)	1,112,517 (61.9)
	LAC	97,601 (4.4)	106,459 (4.1)	86,627 (4.8)
	Africa	45,988 (2.1)	50,186 (1.9)	41,171 (2.3)
	Oceania	16,975 (0.77)	21,677 (0.83)	12,012 (0.67)

LAC: Latin America and the Caribbean; LC: lung cancer. Global Cancer Observatory 2020, International Agency for Research on Cancer, WHO. Accessed January 2021. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf.

Identifying population at risk, when smoking is not the predominant etiology

Targeting the right people for LDCT carries substantial challenge in LMICs due to environmental and biological factors other than smoking, such as radon, asbestos, indoor emissions from open fuel sources, exposure to cooking fumes, and poor ventilation [34]. Lung cancer in nonsmokers is under-recognized and may be driven by oncogenic genetic alterations, such as epidermal growth factor receptor, ALK rearrangement and ROS1. With predominant burden of mutations in Asia and Latin America, the selection of target population for screening becomes challenging [35-38].

Other pulmonary diseases including COVID-19 and tuberculosis

Prevalence of benign, mainly infective, pulmonary diseases presenting with radiographic nodules may result in misdiagnoses [33, 39].

Incidental pulmonary nodule identification

Extensive volumes of chest imaging, including thoracic CT scans and chest X-ray (CXRs), are

Table 3. Stage at diagnosis of lung cancer in developing and developed countries

	Countries	Stage at diagnosis	
		Stage III (%)	Stage IV (%)
LMIC	Mexico [7]	-	98.9*
	India [8]	30.1	64.4
	Peru [9]	9.2	85.5
	Russia [10]	A: 23.7	25.4
		B: 14.1	
	China [11]		42.5*
	Japan [12]	26.5	66.3
	Korea [6]	22.9	42
	Malaysia†	Male: 23	Male: 66
		Female: 19	Female: 71
HIC	U.S. [13]	A: 9.0	45
		B: 17	
	U.K. [13]	A: 13	52
		B: 12	
	Canada‡	20	49

LC: lung cancer; LMICs: low- and middle-income countries; HICs: high-income countries. *Stage IIIB-IV. †Azizah AB. MALAYSIAN NATIONAL CANCER REGISTRY REPORT 2007-2011. Accessed February 24, 2021. Available https://www.crc.gov.my/wpcontent/uploads/documents/report/MNCRRrepor2007-2011.pdf. ‡Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics: A 2020 special report on lung cancer. Toronto, ON: Canadian Cancer Society; 2020. Available at: cancer.ca/Canadian-Cancer-Statistics-2020-EN. Accessed January 20, 2021. https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-cancer-statistics-2020_special-report_EN.pdf?la=en.

routinely acquired through employment health check-ups, immigration checks, tuberculosis screening, trauma, annual check-ups, alongside COVID-19 in recent times. However, these imaging films may be reported in a focused manner to answer the primary clinical question and not scrutinized for the presence of coincidental pathologies or lesions. A real-world study for LC reported that patients being evaluated for another disease or undergoing testing for a routine medical check-up were incidentally diagnosed using a CXR or a CT scan [40]. Patients with incidental LC diagnosis have a higher chance of survival since their cancers are smaller and detected at earlier stages [41, 42]. The complexities associated with detection of IPN(s), compounded by huge workloads and clinical demands especially, but not only in LMICs, amplify the need for optimized detection strategies that can provide opportunities for early detection and intervention.

Evolving role of AI in LC screening

Artificial intelligence can potentially transform healthcare by deriving new and important insights from the vast amount of data generated during the delivery of healthcare every day. Over the past few years, AI has demonstrated increased accuracy and automatic identification of lung radiographic lesions on images captured during intentional screening programs, along with precise identification of possible IPNs in CT scans/CXRs performed for other indications. Recent evidence has demonstrated that deep learning (DL) algorithms can predict the risk of LC with model performances rated on par with radiologists. An end-to-end LC screening with a DL model for predicting LC risk achieved a state-of-the-art performance (94.4% area under the curve) and supported radiologists with absolute reductions of 11% in false-positives and 5% in false-negatives [43]. AI creates an opportunity for incidental identification of known or suspected LC diagnosed at earlier stages. Diagnostic performance of a DL algorithm for detecting LC from a large-scale medical check-up, reported an overall sensitivity of 40% and specificity of 97% for cancer-positive CXR [44]. **Table 4** shows the role of AI for LC diagnosis through screening, incidental identification, or suspected LC [44-49]. AI can provide a trained pair of eyes, reviewing every CXR/CT scan looking for potential lung nodules, thus strengthening the infrastructure and enhancing capabilities of physicians for image interpretation in LMICs. AI can scan CXR and thoracic CT in different settings including primary care, acting as a catalyst for coincidental nodule identification and timely referral for further evaluation.

Opportunities for IPN detection through AI

COVID-19, a unique challenge for LC detection

COVID-19 has disrupted major diagnosis and treatment systems in LC care, leading to an increased time to definitive diagnosis and time to treatment initiation, enhancing the possibility of disease progression [https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/lung-cancer-in-the-covid-19-era, https://journal.chestnet.org/article/S0012-3692(20)30758-3/fulltext]. Due to disruption in screening, thousands of early LCs are expected to be "missed", as patients may present at a later and possibly less treat-

Table 4. Recent studies elucidating the role of artificial intelligence for nodule classification in screening, incidental identification or known or suspected lung cancer

	Author (year)	Objective	Study criteria	Results	Implication
CXR	Nam JG (2019) [45]	● Malignant PN detection	● A DL algorithm developed using 43,292 CXR labelled and annotated by board-certified radiologists ● Algorithmic performance (radiographic classification and nodule detection) validated by one internal and four external datasets	● AI ○ Specificity: 95.2% ○ Sensitivity: 80.7% ○ Rate of false-positive findings per image: 0.30 ● Radiologist ○ Specificity: NA ○ Sensitivity: 70.4% ○ Rate of false-positive findings per image: 0.25	The AI algorithm supported physicians in CXR classification and nodule detection performance for malignant pulmonary nodules and enhanced physicians' performances when used as a second reader
	Lee JH (2020) [44]	● Screening (All individuals underwent CXR as part of comprehensive medical check-up, not for evaluation of specific symptoms or signs)	● Retrospective validation of DL algorithm for LC screening detection on CXR in health screening population ● Validation study: 10,285 CXR ● Health screening cohort: 10,0525 CXR	● Validation results ■ Accuracy: 97% ■ Sensitivity: 64% ■ Specificity: 97% ■ FPR: 3.1% ○ Radiologist ■ Accuracy: 100% ■ Sensitivity: 43% ■ Specificity: 100% ■ FPR: 0.3% ● Health screening results ○ AI classification of cancer-positive CXR ■ Sensitivity: 40% ■ Specificity: 97% ○ AI detection of visible LC ■ Sensitivity: 83% ■ Specificity: 97% ○ AI detection of clearly visible LC ■ Sensitivity: 100% ■ Specificity: 97%	AI algorithm detected LC nodules on CXR with a performance comparable to that of radiologists, which will be helpful for radiologists in healthy populations with a low prevalence of LC
CT Scan	Liu XP (2019) [46]	● Detection of LC nodules in the chest CT	● 5,000 CT images of T1 stage LC patients were used to train an AI algorithm ● 500 CT images were tested by AI algorithm, and the sensitivity and specificity were compared with manual film reading	● Sensitivity: 95.20% ● Specificity: 93.20% ● Kappa value: 0.926, 1	For 1 mm CT sets, the detection rates of AI and manual reading were similar with no significant difference. For 5 mm CT sets, sensitivity of AI was better than manual reading, but the number of false positives increased and the specificity was slightly worse
	Cui S (2020) [47]	● Identifying IPN in LDCT screening as part of routine healthcare	● After the training and validation of a DL algorithm, 64,168 cases were used to retrospectively investigate the prevalence of non-calcified PNs in China by DL algorithm ● All CT images were automatically analyzed by the DL algorithm at first ● Then a junior radiologist checked the result given by the DL algorithm and revised the results when necessary ● Finally, an experienced radiologist confirmed the final decision and issued the diagnostic reports	● Performance: (AUC = 0.86) of AI was better than radiologists (AUC = 0.73) ● Sensitivity: (73%) with AI was lower than radiologists (83%) ● Specificity: (85%) with AI was higher than radiologists (64%)	● AI had better identification sensitivity and performance than radiologists, and was highly consistent with expert radiologists in terms of PN identification, regardless of nodule size ● With good performance, fast processing and efficiency, AI may serve as a radiologist's assistant
	Zhang C (2019) [48]	● Detect and classify PN derived from clinical CT images	● LUNA16 and Kaggle datasets (with CTs obtained during screening) pretrained the AI model ● CT images from 4 hospitals in China trained and validated the algorithm ● Data from 50 patients who underwent surgical resection and had preoperative CT were prospectively collected to assess algorithm	● Assessment of AI algorithm in 50-image evaluation set ○ Accuracy: 92.0% ○ Sensitivity: 96.0% ○ Specificity: 88.0% ● Manual reading ○ Accuracy: 79.6% ○ Sensitivity: 81.3% ○ Specificity: 77.9%	● Compared with manual assessments, AI exhibited significantly better performance in detecting and classifying PN

Zhao L (2020) [49]	Diagnosis of early-stage LC	Included patients undergoing PN surgery with ● Definite surgical pathological diagnosis with staging showing Tis or IA ● Clear and qualified CT data within 1 week before surgery ● SPN with diameter 5 mm to ≤30 mm	● AI ● Sensitivity: 62.8% ● Specificity: 77.8% ● Radiologist ● Sensitivity: 68.3% ● Specificity: 62.8% ● AI+Radiologist ● Sensitivity: 83.3% ● Specificity: 52.8% (P<0.05)	● AI has a better specificity in the diagnosis of early-stage lung cancer, while its sensitivity is not as high as that of radiologists. The combination of the AI+radiologists can obtain higher sensitivity

AI: artificial intelligence; ANN: artificial neural network; AUC: area under curve; CI: confidence interval; CXR: chest X ray; CT: computed tomography; DL: deep learning; LDCT: low-dose computed tomography; PN: pulmonary nodule; SPN: solitary pulmonary nodule.

able stage, once the pandemic lifts. The impact will potentially mean poorer survival for patients with delayed diagnosis. In such circumstances, although patients are being treated within the health system for COVID-19, lack of an organized pathway for evaluating IPNs may cause a missed opportunity for early diagnosis and increased risk of LC progression. Although the COVID-19 pandemic is a crisis, it also presents an opportunity. Primarily a respiratory pathogen, COVID-19 is yielding large numbers of CT scans and CXR during its evaluation and management in ambulatory and hospitalization setting, as well as for follow-up of patients with sequela of pulmonary disease [50-53]. Furthermore, many of the at-risk patients for COVID-19 (advancing age, smokers) are the same population at-risk for LC. This represents a pivotal opportunity to screen radiographic images for IPN detection, thus potentially bridging the gap for diagnosing LC in LMICs. However, radiographically COVID-19 and early LC may show as ground-glass opacities, with similar but independent features [54]. This could inadvertently lead to a missed opportunity for reporting an incidental LC at an early stage, especially under the clinical pressures posed by such a severe pandemic with overwhelmed health systems. AI could be used as a second reader of CXRs and thoracic CT scans to identify non-infective pulmonary nodules, which otherwise might be overlooked (**Figure 1**).

Tuberculosis and other lung diseases

Higher background prevalence of benign, mainly infective, pulmonary diseases presenting with radiographic nodules (particularly with plain CXR) enhance risk of LC lesions being wrongly attributed as nonmalignant conditions-resulting in misdiagnoses or delayed diagnoses [33, 39]. In LMICs endemic for tuberculosis such as Philippines, India, Malaysia, and Latin America countries, capitalizing on the vast numbers of thoracic images obtained from routine mass screening, offers yet another opportunity for IPN findings. However, requirement for specialist training may mean that some small IPNs remain misdiagnosed as tuberculosis. AI-assisted tools can scan large volumes of thoracic images performed for tuberculosis or other lung conditions, including but not limited to emphysema and other signs associated with obstructive pulmonary diseases, bronchitis, pneumonia, and facilitate easy identification of IPN.

Other conditions

Imaging in cases of trauma including fractures and dislocations, though commonly available, is often overlooked for pulmonary lesions in primary healthcare settings. Navigating the trauma related images through AI can identify hidden IPNs for early LC detection. Similarly, imaging for fibrosis or interstitial lung diseases can be leveraged to extract information of insidious IPNs.

Healthy individuals

Annual medical and employment health checks routinely provide an abundance of thoracic imaging which can be explored through AI-assisted technology to identify IPNs. AI systems can help overcome limitations of human vision by detecting lung spots invisible to the naked eyes, thus shifting burden from busy specialists.

Case studies for IPN detection through AI

To evaluate the benefits of AI-assisted IPN detection and subsequent early LC diagnosis in resource-constrained LMICs, pilot model initiatives are being conducted in Russia, Latin America, and Asia through collaborations between AstraZeneca, healthcare institutions

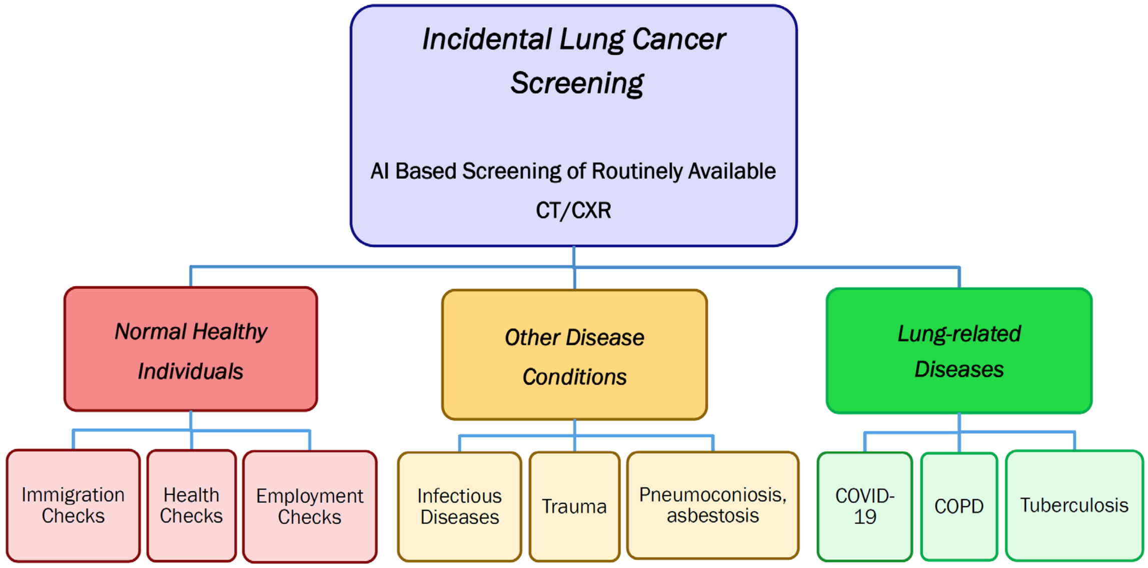

Figure 1. Opportunities for incidental pulmonary nodule detection through artificial intelligence. CT: computed tomography; CXR: chest X-ray; COPD: chronic obstructive pulmonary disease.

and AI enabled solutions. The fundamental design and pathway of the studies are illustrated below.

Russia

Pilot projects are being conducted for evaluating AI-assisted IPN detection using chest CT scans from different regions of Russia for COVID-19-related reasons (**Figure 2A**). The major goals included reassessment of COVID-19 chest CT database to reveal IPNs, possibly indicative of a co-existing cancer, thus increasing chances of early LC diagnosis.

Design: Retrospective approach.

Pathway: Utilizing the local CT scan database, anonymized patient data were subjected to AI analysis. The AI tool highlighted cases for expert assessment, which could otherwise have been missed during traditional workflow. Suspicious LC cases segregated after expert evaluation were de-anonymized and sent to experts for validation and confirmation. It is important to understand usability of AI technology for malignant node detection in case of simultaneous significant COVID-related signs of pneumonia. According to published data from Moscow COVID-19 chest CT database, 50% are without COVID-19 signs (CT-0) and 50% have COVID-19 changes, of which 61% have CT-1 (<25% lung affected), 30% have CT-2 (25%-50% lung affected), 8% have CT-3 (50%-75% lung affected), and 1% have CT-4 (>75% lung affected). That is why there are two parallel groups in pilot programs, which include and exclude patients with CT 3-4 for AI assessment [55].

Long-term goal: Encouraging results of the pilots may drive full implementation of AI-assisted analysis of the COVID-19 CT database for evaluating new LC cases on a national scale, alongside analysis of CT scans in routine clinical practice-even in post-COVID-19 times. To this end, implementation of prospective nationwide LC screening programs in routine practices, LC screening awareness campaigns in post-COVID era, and LC screening education for healthcare provider's/key external experts, are deemed as crucial steps going forward.

Latin America

Based on the same principles, an AI-assisted tool is being used in Latin America for the evaluation of CXRs in primary care settings, across more than 10 countries, including Brazil, Mexico, Argentina, Chile, Colombia, Costa Rica and Panamá among others (**Figure 2B**). Challenges for implementation of different health programs, alongside changes in priorities due to COVID-19 pandemic, have delayed progress in the initiation of LC screening proj-

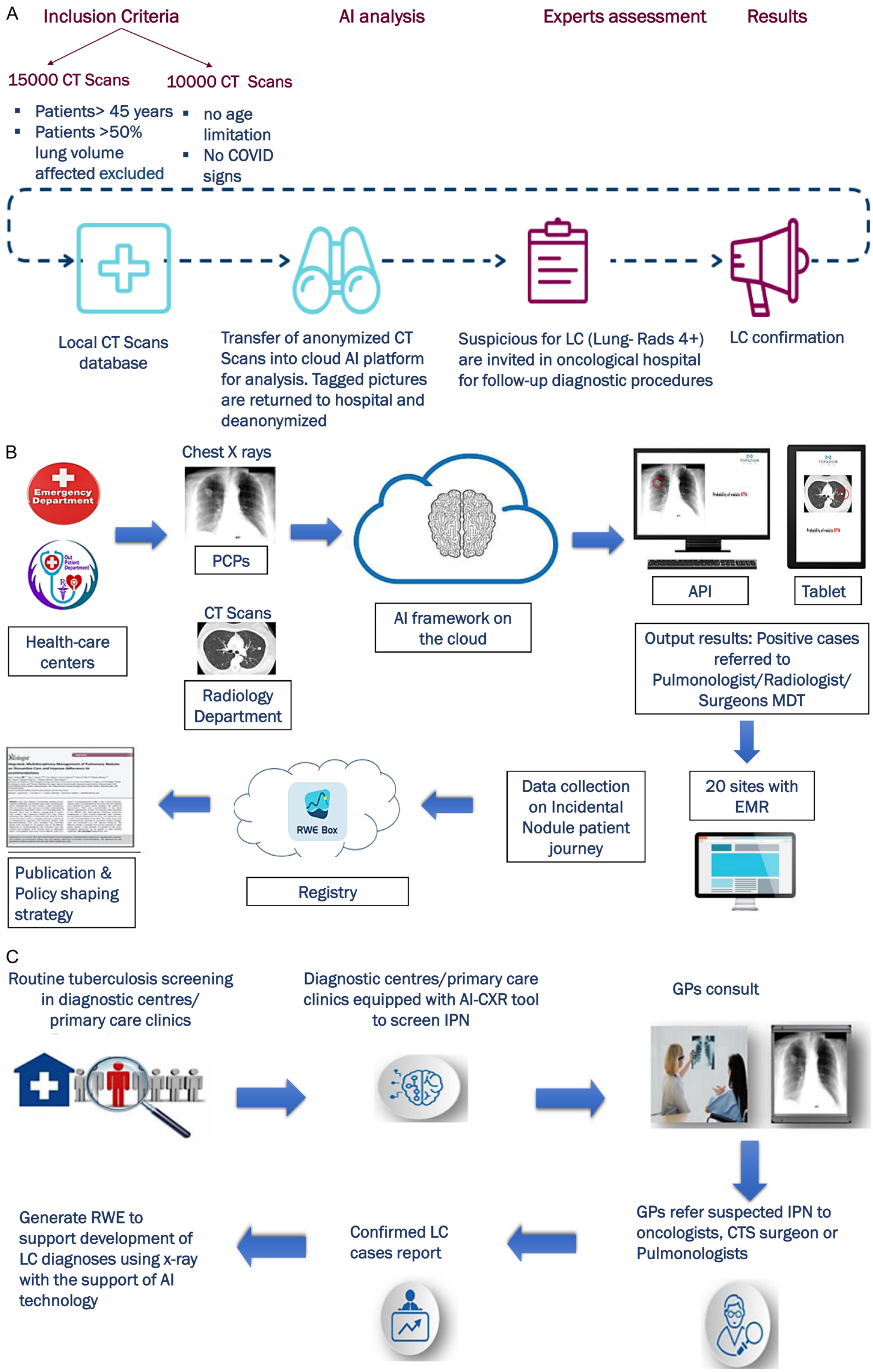
A
Inclusion Criteria
AI analysis
Experts assessment
Results
15000 CT Scans
10000 CT Scans
Patients> 45 years
Patients >50% lung volume affected excluded
no age limitation
No COVID signs
Local CT Scans database
Transfer of anonymized CT Scans into cloud AI platform for analysis. Tagged pictures are returned to hospital and deanonymized
Suspicious for LC (Lung- Rads 4+) are invited in oncological hospital for follow-up diagnostic procedures
LC confirmation
B
Emergency Department
Health-care centers
Chest X rays
PCPs
CT Scans
Radiology Department
AI framework on the cloud
API
Tablet
Output results: Positive cases referred to Pulmonologist/Radiologist/ Surgeons MDT
20 sites with EMR
Data collection on Incidental Nodule patient journey
RWE Box
Registry
Publication & Policy shaping strategy
C
Routine tuberculosis screening in diagnostic centres/ primary care clinics
Diagnostic centres/primary care clinics equipped with AI-CXR tool to screen IPN
GPs consult
GPs refer suspected IPN to oncologists, CTS surgeon or Pulmonologists
Confirmed LC cases report
Generate RWE to support development of LC diagnoses using x-ray with the support of AI technology

Figure 2. A. Case study of artificial intelligence assisted incidental pulmonary nodule detection in Russia. AI: artificial intelligence; CT: computerized tomography; LC: lung cancer. B. Case study of artificial intelligence assisted incidental pulmonary nodule detection in Latin America. AI: artificial intelligence; API: application programming interface; CT: computerized tomography; LC: lung cancer; MDT: multidisciplinary team; PCP: primary care physician; RWE: real-world evidence. C. Case study of artificial intelligence assisted incidental pulmonary nodule detection in Asia. AI: artificial intelligence; CTS: cardiothoracic surgeons; GP: general practitioner; IPN: incidental pulmonary nodule; LC: lung cancer; RWE: real-world evidence.

ects in the region. This AI-assisted model was aimed to collect additional evidence on advantages of a combined approach of LC screening and IPN detection, through a pilot of 20 clinics that are capturing data about health resources utilization, time to definitive diagnosis, and stages for the positive cases.

Design: Prospective.

Pathway: By utilizing the existing algorithm for detecting radiological signs, such as atelectasis, cardiomegaly, pleural effusion, pneumonia, tuberculosis, and COVID-19, the CXRs and CT scans obtained by health centers, but also at the primary care setting, are subjected to AI-based analysis for nodule detection. The tool could be used from a mobile phone application, allowing the adoption even in settings where image digitalization is not available. The resultant output delineating the positive cases is obtained in real-time, allowing the immediate referral to a multidisciplinary team of experts, including pulmonologists and radiologists. The electronic medical records from 20 sites encompassing data on IPNs are assimilated onto a real-world registry for further analysis and policy shaping.

Long-term goal: Prospective data collection, with expansion in primary care settings, is regarded imperative for using AI in the real-world clinical practice going forward.

Asia

Philippines and Malaysia are leading a similar initiative for early LC diagnosis, with plans of expansion to Thailand, Vietnam, and India (**Figure 2C**). In many parts of Asia, patients undergo routine tuberculosis screening in diagnostic centers or primary care clinics as part of the immigration or employment process. Because of lack of attention for LC and tools for timely identification of the suspected cases, general practitioners may delay the referral of patients to specialists, resulting in delayed diagnosis.

Design: Prospective.

Pathway: The program targets the chain of diagnostic centers and primary care clinics conducting routine tuberculosis and health screening for judicious utilization of resources in the health system. The diagnostic centers/primary care clinics are equipped with AI and leverage AI-CXR to regularly process CXRs to screen incidental findings and raise awareness for the need for further assessment. As most IPNs are not adequately followed up, the program links the facilities to healthcare centers to allow timely assessment, diagnosis and treatment. By linking the stakeholders together, the program aims to close the loop for patients and ensure accurate and early diagnosis, intervention, and improved patient outcomes.

Long-term goal: Going forward, the program plans to focus on real-world evidence (RWE) generation to navigate LC diagnoses using CXR supported by AI technology.

Evidence from a retrospective study from India has shown diagnostic accuracy of a computer-assisted diagnosis (CAD) software for automated CXR interpretation of tuberculosis; sensitivity and specificity of CAD software were 71% and 80%, compared with those of radiologists at 56% and 80%. The controls had a high prevalence of other lung diseases causing radiological manifestations, such as lung malignancy (15%) [56]. Such malignant nodules might be overlooked, especially where tuberculosis burden is high and the ratio of skilled radiologists to people is low. However, strategic programs for AI-assisted detection of IPNs, facilitated by linkages to healthcare experts for timely follow-up, can support early diagnosis and improved patient outcomes.

Potential advantages and challenges of AI in LC screening and diagnosis

SWOT analysis illustrating the strengths, weakness, opportunities, and threats for AI-assisted IPN detection in LMICs is shown in **Figure 3**.

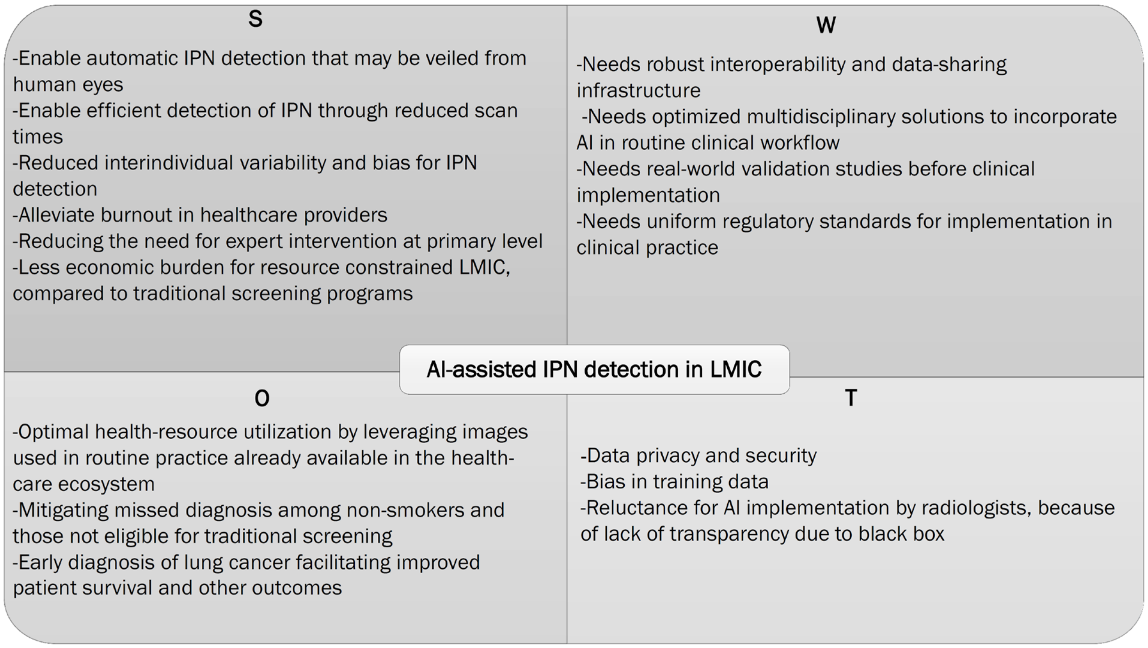

Figure 3. SWOT analysis illustrating the strengths, weakness, opportunities and threats for AI in lung cancer detection. AI: artificial intelligence; S: strength; W: weakness; O: opportunity; T: threat; IPN: incidental pulmonary nodule; LMICs: low- and middle-income countries.

Strengths and opportunities

Enhanced accuracy, efficiency, and precision: The ability to rapidly sift through high volumes of imaging and precise quantification of information from images likely to be missed in traditional care makes AI an efficient assistant to radiologists [43]. AI can drive accurate image interpretation, even in primary healthcare, thus empowering and reinforcing the skills of manpower in LMICs. Predicting malignancy risk accurately may help reduce time taken to achieve confirmatory diagnosis, risk of false-negatives, and psychological stress for patients with benign pulmonary nodules.

Reduced inter-individual variability and bias: AI-aided diagnosis can improve consistency and reduce interpreter variability in assessing and reporting LC risk among radiologists and pulmonary medicine physicians [57]. AI can be vital for less experienced/nonspecialized clinicians to help classify the malignancy risk of lung nodules, allowing a quantifiable and reproducible interpretation [https://arxiv.org/abs/1807.07455v2]. An AI-based system can objectively and consistently account for radiological parameters such as nodule size, margins, and attenuation [58].

Reduced burden for healthcare providers: AI can help radiologists read images effectively, by scanning an entire CT image in less than a minute and providing complementary interpretation, highlighting areas of the scan requiring particularly close inspection. This information may help avoid fatigue- or workload-induced missed diagnoses and can be invaluable in helping address shortage of trained radiologists in LMICs. Classification of an imaging study as "low risk" or "normal" by an AI system allows radiologists to focus their time and attention on CXRs/CT scans of cases requiring a closer examination [59].

Enhanced democratization and healthcare cost-effectiveness: AI confers a key advantage by providing access to rapid, affordable, radiological "opinion" especially in countries where radiology expertise is scarce, and can extend to the level of every hospital and primary care clinic, even in remote, under-served areas. Therefore, AI can be a step forward in breaking down barriers to universal health coverage and access. Since AI can help reduce the false-positive rate, it enables cost-effective LC screening by reducing over-diagnosis and the follow-up costs for additional scans and biopsies of benign nodules [43].

Mitigating missed diagnosis and optimal health-resource utilization: The traditional screening algorithm has stringent eligibility criteria, focusing on high-risk individuals. AI-assisted IPN detection can identify people ineligible for traditional screening, such as non-smokers and those with genetic mutations. Traditional LC screening programs may incur huge costs on the health-systems, thus decreasing the feasibility of successful implementation in resource-constrained countries. Leveraging AI for routinely available images for IPN detection results in optimized health-resource utilization and ultimately less economic burden for resource-limited LMICs.

Weaknesses and threats

Need for real-world validation studies before clinical implementation: Heterogeneity in algorithms, predictive models, and training datasets affect reproducibility and generalizability. Most studies have been retrospective, using historic data to train algorithms; the true utility comes to the fore in the real-world setting, which may vastly differ from that experienced in the algorithm training [60]. However, the lack of real-world validation is rapidly being addressed with many studies (ongoing/completed) integrating AI validation in their study design. AI tools for the identification of IPNs should be deployed initially as educational aids for primary care physicians and not as CAD, followed by well-designed pilot projects and RWE studies or registries for collecting additional data in the real-world setting.

Privacy and data protection: Issues related to data privacy, especially for sensitive data medical information, are paramount. The Health Insurance Portability and Accountability Act in the U.S. and the General Data Protection Regulation in the European Union requires the protection of individuals' medical records and other 'personal health information' recorded in any medium [61]. Hence, the adoption of privacy-centered technical and regulatory standards, focusing on security, privacy protection, and ethical use of sensitive information to ensure both humane and regulated management of patients is warranted.

Regulatory oversight: When intended to diagnose, treat, or prevent health problems, AI-based software is defined as a medical device under the US and the European regulatory bodies [61, https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf]. Based on the risk of the devices, the Food and Drug Administration (FDA) provides approval through three approaches: premarket approval pathway (high-risk devices), de novo premarket review (low- and moderate-risk devices), and 510 (k) pathway. Similarly, in Europe, devices of high-risk classes are handled by private Notified Bodies that issue a Conformité Européenne (CE) mark for approval. Uniform standards for the implementation of AI in healthcare are not yet established; however, regulatory bodies such as the FDA and European Medicines Agency are actively pursuing a dialogue with all stakeholders to evaluate use of AI algorithms in routine clinical practice [61]. AI models will be subjected to intense scrutiny for validated training datasets, intended use, robustness and generalizability of outputs before approvals.

Determining clinical significance: Implementing AI algorithms confirmed to have high sensitivity and specificity, alongside clinician verification of identified IPNs are the cornerstone to optimize treatment planning. Incidental LC findings detected by AI need to be carefully aligned in the correct clinical context, to avoid patient stress, healthcare costs, and undesired side effects from treatment. "AI chasm" reflects the gap between accuracy and clinical efficacy, highlighting the role of medical experts in discerning whether the incidental findings are clinically significant, especially during the early phase of AI implementation [62].

Roadmap-way forward for AI-assisted IPN detection in LMICs

Firstly, the identification of potential partners and stakeholders from the AI industry and healthcare sector to promote widespread access across the tiers of health-system, especially the primary care, is critical. Involvement of healthcare providers through targeted training can help catalyze the adoption of AI-assisted IPN detection in routine workflow in LMICs. Building sustainable platforms with robust infrastructure is essential to maintain stakeholder support and maximize the long-term effects of AI technology (**Figure 4**).

Secondly, comprehensive, multidisciplinary care is an ideal setting to improve access to

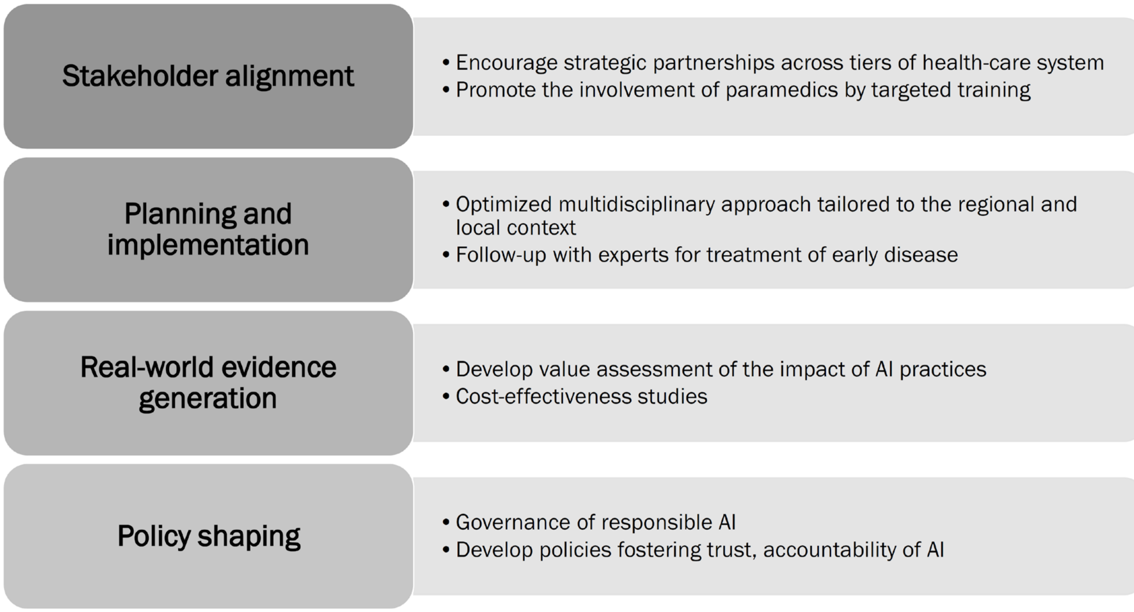

Figure 4. Roadmap for artificial intelligence assisted incidental pulmonary nodule detection in low- and middle-income countries. AI: artificial intelligence.

AI-assisted IPN detection for early LC diagnosis, particularly in underserved populations. Optimizing the pathway through the identification of good practices about implementation, formulation of guidelines tailored to the region, and collaborative sharing of information can lead to increased efficiency. Notwithstanding the importance of early detection, careful evaluation and follow-up with experts is needed to avoid missing early LCs and interventions on potentially morbid benign nodules. Considering the complexity of managing these patients, counseling and shared decision-making are critically important.

Thirdly, real-world prospective studies validating the value and impact of AI-assisted IPN detection in improving patient care should be conducted. Such studies can also provide insights on the challenges and barriers for clinical implementation in routine practice. In addition, evidence is needed on whether these strategies can optimize heath-resource utilization in terms of economic costs among less-resourced settings and mitigate the effects of financial constraints, compared with traditional care pathway.

Conclusion

In the face of rapid changes and increasing uncertainty in healthcare, the ability to improvise and use resources judiciously has become more critical than ever. Alongside the challenges associated with unmet needs for health problems such as poor outcomes of LC patients in LMICs, mainly due to late stages at diagnosis. Recently COVID-19 has had a devastating effect on our society-we can transform this unprecedented circumstance to an opportunity by novel technology of AI. The use of AI in the evaluation of pulmonary images can improve the accuracy for identifying IPNs in primary care settings, leading to a shift in the stage when LC is diagnosed. To improve lung cancer survival, it is crucial that patients are diagnosed at an early stage when the chances of cure are highest. This is especially true in LMICs where most patients are diagnosed at an advanced and usually incurable stage. AI-assisted IPN detection can mitigate the challenges associated with identifying populations for screening and decrease the economic burden by optimizing health-resource utilization. In addition, AI can increase the incidental identification of LC nodules on images taken for non-cancerous reasons, such as health checks, immigration, tuberculosis screening, and, more recently, the current COVID-19 pandemic. Because of the challenges of conducting organized LC screening programs in LMICs, AI-assisted IPN detection could be an important step forward in the battle to diagnose LC earlier and improve patient outcomes.

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Disclosure of conflict of interest

SG is Medical Director at AstraZeneca, LatAm Area; PC is Head of Oncology, International Medical at AstraZeneca and MB is Therapeutic Area Lead, Russia, at AstraZeneca.

Abbreviations

AI, artificial intelligence; CAD, computer-assisted diagnosis; CE, Conformité Européenne; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease of 2019; CXR, chest X-ray; CT, computed tomography; FDA, Food and Drug Administration; LMIC, low- and middle-income countries; LC, lung cancer; IPN, incidental pulmonary nodules; LDCT, low-dose computed tomography; USPSTF, United States Preventive Services Task Force; SWOT, Strengths weakness opportunities and threats.

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