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## Screening Tackles the Big Three: the AGILE Alliance

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There is growing awareness of the potential of low-dose CT (LDCT) to screen for the three major causes of death in adults (1). These are heart disease, COPD, and lung cancer. Currently, there is acceptance of LDCT screening for lung cancer where the benefit was initially shown by a prospective cohort study in 1999 by the Early Lung Cancer Action Program (ELCAP) (2) and subsequently confirmed by the results of two large, randomized trials, the National Lung Screening Trial (NLST) and the Netherlands–Leuven Longkanker Screenings Onderzoek (NELSON) trial as well as an international meta-analysis (3, 4, 5). National

programs have been implemented in many countries around the world and others have begun pilot programs. European countries are developing LCS practice at the population level following the Institutional endorsement by the Europe's Beating Cancer Plan (6). On the other hand, the European population favors receiving a comprehensive health check that includes diffuse bronchopulmonary disease and cardiovascular risk (7). Coronary artery calcification (CAC) scoring has been gaining acceptance as a screening tool and included in guidelines by the American Heart Association and American College of Cardiology (AHA/ACC) (8) in the United States and by the European Society of Cardiology (ESC) (9) for people with intermediate risk. While evidence accumulates regarding benefits associated with this test, results from ROBINSCA, a European RCT are awaited before firmer recommendations can be made (10). Regarding COPD, according to the United States Preventive Services Task Force (USPSTF), there is no evidence of benefit in screening for COPD receiving a "D" recommendation. This means that, "The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits" (11). However, the USPSTF has not yet evaluated the benefit of screening for emphysema with thoracic CT in a tobacco-exposed cohort. For purposes of this editorial, screening for lung cancer, emphysema and coronary artery disease will be referred to as screening for, "The Big Three."

There are growing numbers of countries with guideline recommendations for LDCT screening for lung cancer, some with governmental coverage (12). CAC screening, while included in guidelines in many countries, is not formally covered by insurance except in limited circumstances (13). Currently, there are no countries which recommend COPD screening. However, in the context of real-world LDCT lung cancer screening, there is no consensus whether to share information provided by LDCT about emphysema and cardiac findings. In fact, in many countries there is concern regarding whether the full radiological information available from a chest CT should even be reported. With the ever increasing availability of large databases and advances in artificial intelligence, these concerns take on increased urgency as the capability to make additional predictions, even beyond the Big Three finding will raise many ethical issues (14).

In the United States, CAC scores and even emphysema scores are routinely reported in the context of LDCT lung cancer screening, typically in semi-quantitative terms by visual scoring (15, 16), although there is no additional reimbursement for these findings. In some countries, they are specifically not reported and only lung screening results are described. Considerations regarding reporting findings beyond what the test was initially meant to evaluate has been a long simmering controversy.

In the setting of lung cancer screening, the two additional frequently lethal conditions, emphysema and coronary artery disease which have overlapping risk factors with lung cancer can be readily evaluated. This additional radiological information is available without additional radiation dose, no additional scanner time, and no additional time imposition on the screening participant. The only question is how it should actually be reported. In the United States under a recent legislation (21<sup>st</sup> Century Cures Act) all such diagnostic information stored in the electronic medical record has to be discussed with the person undergoing the medical test (17). Regarding emphysema, this topic has recently been reviewed, and two studies of large screening populations demonstrated that the majority of screening participants found to have emphysema were unaware that they have the disease (18, 19). Emphysema is not reversible and there is no suggested treatment, especially in asymptomatic subjects. Yet, emphysema represents a

biomarker of susceptibility to lung damage, therefore it can contribute to prognostic stratification (including risk of LC as well as respiratory morbidity). For this reason, the authors here, strongly advocate for a conversation with the person having the LDCT and to discuss the diagnosis and outline potential preventive interventions including enhanced smoking cessation or increased physical activity.

It is for these concerns that two large lung cancer screening consortiums in the United States (I-ELCAP) and Europe (I-DNA) decided to collaborate to forge a new organization, the Alliance for Global Implementation of Lung and Cardiac Early disease Detection and Treatment (AGILE<sup>DXRX</sup>) with the following mission statement:

The early detection of lung cancer using thoracic CT has been widely demonstrated in multiple international trials to objectively increase cure rates. Now the international focus is on effective and economical implementation. Increasingly, it is emerging that thoracic CT screening is also detecting a range of early tobacco-related diseases including cardiovascular disease and chronic obstructive pulmonary disease. These three diseases comprise the 'BIG3', as they collectively account for close to half of the premature deaths globally. Thoracic CT screening presents a unique opportunity to integrate care for this high risk cohort with a single imaging examination. We plan to develop optimized protocols for evaluation of these major diseases, explore challenges and define solutions in enabling implementation, especially for economically disadvantaged countries across the world. A core strategy in achieving this ambitious goal is to leverage the use of AI processes across the continuum of care, including its use for risk assessment, disease detection and managing disease interventions.

AGILE held its first meeting on May 9-11, 2024 at the Universidad de Navarra in Madrid, Spain. Its next meeting will be held on April 3-5<sup>th</sup>, 2025 at the Princess Srisavangavadhana College of Medicine in Bangkok, Thailand (20). The meetings primarily focus on integration of the BIG Three major illnesses with a view towards comprehensive evaluation both from an imaging standpoint as well as clinically. The critical role of imaging is foremost in these meeting with a special interest on image quality and its impact. In addition, the meetings take a more holistic approach regarding the information that is available in these images, even beyond the Big Three, such as osteoporosis, abnormal adiposity, steatosis, and muscle mass and quality. Finally, the meetings recognize the critical role of therapeutics, and the need to consider this as inseparable from screening, meaning that the screening process does not end at early diagnosis, but rather, needs to consider therapeutic options and their usefulness as preventive measures as well. The meeting also includes case review sessions both for diagnostics and therapeutics with a view towards bringing out cutting edge concerns where there are differences of opinions in how to proceed among experts.

Finally, the meeting is meant to foster collaborative work with inputs on a global scale to develop independent recommendations for scanning and management protocols and even considerations for how to further integrate imaging findings into therapeutic considerations. Collaborations with existing organizations will be pursued and meetings will be available at no charge on Zoom with recordings available afterwards as well.

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