Virtual Human Twins in Lung Health: A Comprehensive *In Silico* Screening Approach

Fakrul Islam Tushar[1,2], Liesbeth Vancoillie[1], Cindy McCabe[1,3], Amareswararao Kavuri[1], Lavsen Dahal[1,2], Brian Harrawood[1], Milo Fryling[1], Mojtaba Zarei[1,2], Saman Sotoudeh-Paima[1,2], Fong Chi Ho[1,2], Dhrubajyoti Ghosh[4], Michael R. Harowicz[1], Tina D. Tailor[1], Sheng Luo[4], W. Paul Segars[1,2,3], Ehsan Abadi[1,2,3], Kyle J. Lafata[1,2,3,5], Joseph Y. Lo[1,2,3*], Ehsan Samei[1,2,3*]

[1] Center for Virtual Imaging Trials, Carl E. Ravin Advanced Imaging Laboratories, Dept. of Radiology, Duke University School of Medicine

[2] Dept. of Electrical & Computer Engineering, Pratt School of Engineering, Duke University

[3] Medical Physics Graduate Program, Duke University

[4] Dept. of Biostatistics and Bioinformatics, Duke University School of Medicine

[5] Dept. of Radiation Oncology, Duke University School of Medicine.

[*] These authors contributed equally as co-senior authors.

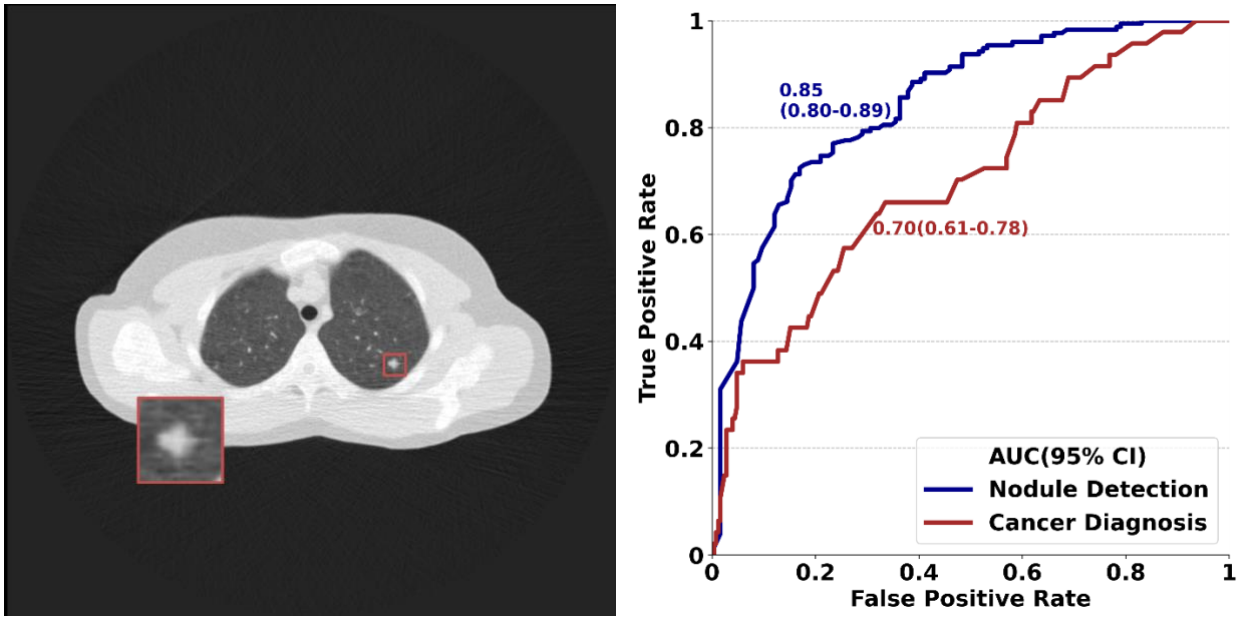
Purpose: To enhance lung cancer screening by integrating in silico trials with statistical modeling, minimizing traditional trial limitations such as cost, time, and radiation exposure. This approach simulates the entire imaging chain and diagnostic process, improving screening efficiency and accuracy.

Methods and Materials: We created 313 unique virtual patient models based on actual patients with mean age of 59 ± 14 years with 44% female representation. Within this cohort, 174 models include a total of 512 digitally inserted lung nodules, distributed between uniform (n=202) and variable (n=310) textures, with a range of diameters to mirror the distribution in the National Lung Screening Trial (NLST) for true-to-life simulation. The virtual cohort was digitally imaged employing a verified CT simulation software, and subsequently reconstructed with the agnostic MCR toolkit, ensuring broad applicability and adherence to standard imaging protocols. Our virtual reader emulates clinical diagnostics by combining detection and classification in a 3D AI model. Simulated nodules were "statistically labeled" as benign or malignant with random probability informed by radiomics features, thus facilitating the important transition in tasks from nodule identification to cancer diagnosis. The primary outcome focused on the variation in the Receiver Operating Characteristic Area Under the Curve (AUC) for both patient-level nodule detection and cancer diagnosis, supplemented by a detailed lesion-level analysis within sub-groups.

Results: Using the *in silico* pipeline on a parallel computing cluster, we produced 1,878 simulated chest CT scans in 52 hours, averaging 36 scans per hour. Analysis of 313 virtual patients yielded a patient-level nodule detection AUC of 0.85 (95% CI: 0.80-0.89), compared to the more difficult task of cancer diagnosis with AUC of 0.70 (95% CI: 0.61-0.78). Subgroup evaluations revealed that the virtual reader model was more effective in identifying homogeneous lesions (AUC 0.97) than heterogeneous lesions (AUC 0.71), with particularly high performance for nodules larger than 8 mm (AUC 0.98).

Conclusion: Our research demonstrates the value of in silico trials in enhancing the calibration and efficacy of imaging-based diagnostic technologies. Our statistical labeling of simulated lung nodules demonstrates a new approach to bridge in silico trials toward clinically relevant endpoints. Future work will also consider the additional in silico modeling of demographic and clinical data.

Clinical Relevance: This study confirms the practicality of in silico trials and their potential to enhance diagnostic accuracy, directly informing the advancement of imaging techniques and patient care strategies in lung health.



(a) **(b)**

Figure 1. (a) Example of a simulated virtual chest CT scan image replicating the imaging properties of representative NLST-era CT technology with a simulated nodule marked in red and shown in insert. (b) Area Under the ROC (AUC) for patient-level nodule detection (**blue** ROC) and cancer diagnosis (**brown** ROC) performance of AI model acting as virtual reader. Cancer diagnosis performance utilizing proposed statistical labeling aligns with reported clinical datasets.