The need for high sensitivity biomarkers in lung cancer screening: results of a modelling study

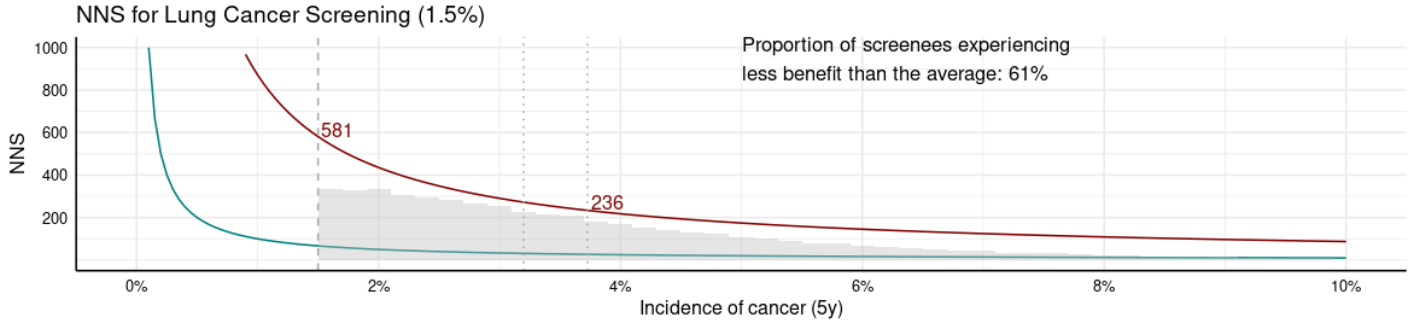
Ben Jacob, Patrick Redmond
RCSI University of Medicine and Health Sciences, Dublin, Ireland

Background: The National Lung Screening Trial demonstrated an apparent all-cause mortality benefit of low dose CT (LDCT) screening for individuals at high risk of lung cancer, while numerous meta-analyses have irrefutably demonstrated a 15-20% reduction in lung cancer mortality. Current USPSTF guidelines recommend lung cancer screening (LCS) for 50–80-year-olds with a 20 pack-year smoking history and no more than 15 years since their last cigarette. Many authors have argued that such simplistic eligibility criteria exclude some high-risk individuals while including low-risk individuals for whom the benefits of LCS are outweighed by the harms. “Risk-based screening”, which takes account of a greater number of factors allowing risk (i.e. lung cancer incidence) to be more accurately calculated, is believed to improve candidate selection, and, therefore, the efficacy of screening.

Aim: The aim of this modelling study is to show that even risk-based screening does not sufficiently acknowledge that the individuals just above the screening threshold (e.g., 1.5% incidence over 5 years, used in PLCOm2012 based screening strategies) likely receive more harm than benefit.

Methods: In this simulation study, we calculate the benefit of screening in an LCS-eligible population as a function of predicted incidence. Benefit is operationalised as “the numbers needed to be screened to prevent one lung cancer death”. Other parameters such as the lung cancer mortality with screening versus standard care are calculated from meta-analysis data from Sadate et al (2020). A second phase models the post-test probability of a negative biomarker test (used to further characterise intermediate risk individuals) as a function of predicted incidence, test sensitivity and test specificity.

Results: As can be seen in Figure 1, which utilises typical estimates for model inputs, e.g. a RR of lung cancer mortality of 0.83, the NNS (red line) varies greatly according to cancer incidence, even in a specially selected eligible population (the grey distribution, greater than 1.5% risk). Critically the “overall benefit” typically quoted to patients during the consent process (i.e., the NNS calculated from the mortality benefit seen in the eligible cohort as a whole) is received by less than half of the LCS participants.



Implications: We argue that intermediate risk LCS candidates should be offered testing with an early detection biomarker, to further characterise their risk before proceeding to LDCT. Crucially, we will illustrate the sensitivity of the biomarker test required to adequately rule out the need for LCS in these individuals, creating a novel well-defined use case for lung cancer biomarkers.