



# WHY SHOULD LC SCREENING BE IMPLEMENTED IN EUROPE

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In January 2020, the NELSON trial published as second largest lung cancer screening trial their mortality results. The positive results of both the Dutch-Belgian screening trial (NELSON; n=15,792), with relatively low referral rates, and the NLST (n=53,454) in the USA provided conclusive evidence now.

In the NELSON trial, 13,195 males and 2,594 females aged 50-74 at high risk for developing lung cancer were included in the screen (4 CT screens) or control arm (usual care). On average, 9.2% of the screened participants underwent at least one additional CT scan (initially indeterminate). The overall referral rate for suspicious nodules was only 2.1%. At 10 years of follow-up, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group; lung-cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively. The cumulative rate ratio for death from lung cancer at 10 years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; P = 0.01) in the screening group as compared with the control group. Among women, the rate ratio was 0.67 (95% CI, 0.38 to 1.14) at 10 years of follow-up.

However, although the positive results of two large-scale RCTs, implementation is likely to be limited, slow and of variable quality throughout Europe, and current guidelines could easily require up to 25 million CT screens annually. The most optimal strategy in risk-based lung-thoracic screening is still unknown regarding the optimal and most cost-effective (e.g., targeted) strategy 1) to recruit, 2) to integrate smoking cessation and co-morbidity-reducing services, and 3) to determine the (risk-based) screening interval. Personalised regimens based on the baseline CT result can potentially retain 85% of the mortality reduction achievable through screening at 45% less screens, thus potentially saving much unnecessary harm associated with screening, and 0.5-1 billion Euros per year.

**4-IN-THE-LUNG-RUN** (TOWARDS INDIVIDUALLY TAILORED INVITATIONS, SCREENING INTERVALS, AND INTEGRATED CO-MORBIDITY REDUCING STRATEGIES IN LUNG CANCER SCREENING) is the first multi-centered randomized-controlled trial on the implementation of volume CT lung cancer screening amongst 24,000 males and females, at high risk for developing lung cancer, across five European countries. The heart of 4-IN-THE-LUNG-RUN is evaluating whether it is safe to have risk-based less intensive screening intervals after a negative baseline CT. Various methods to improve participation of hard-to-reach individuals will be assessed in five different healthcare settings. Innovative co-morbidity reducing

strategies will be tested including other markers on CT imaging, as Calcium Score and COPD. Cost impact and cost-effectiveness analyses using a natural history model will steer implementation. 4-IN-THE-LUNG-RUN addresses key questions for large-scale introduction of risk-based lung and thoracic CT scanning in Europe and worldwide (“for in the long run”). We envisage that with the answers to questions established by this trial, many European citizens will swiftly benefit from this high-quality screening technology, others will face less harms than previously anticipated, and health care costs will be reduced to a large extent.

**4-IN-THE-LUNG-RUN** is performed by a multidisciplinary consortium of leading experts in the field of population-based cancer screening, CT imaging, biomarkers, treatment, modelling, and understanding health behaviour, and in both new and existing high quality centres.

The experienced consortium will strongly interact with key stakeholders, and discuss interim results with key other international initiatives on CT screening, biomarkers, and smoking cessation practices. This proposal will form the evidence base for risk-based lung cancer screening with huge benefits for the EU, on health outcomes, cost savings, and innovation in the long run.