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Editorial

EDITORIAL

Basing Eligibility for Lung Cancer Screening on Individualized Risk Calculators Should Save More Lives, but Life Expectancy Matters

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It is infeasible to conduct randomized trials for each possible screening recommendation. Thus, mathematical or statistical modeling is the only immediately available way to inform guidelines groups about the potential effect of possible screening recommendations for novel screening programs. In particular, in the wake of the landmark National Lung Screening Trial (NLST) (1), Cancer Intervention and Surveillance Modeling Network (CISNET) researchers provided microsimulation-modeling results to the US Preventive Services Task Force (USPSTF) on the potential number of lives saved and life-years gainable, for different eligibility guidelines based on combinations of age, pack-years (packs per year multiplied by number of years of smoking), and number of years since quitting smoking (2). The USPSTF recommended eligibility criteria similar to that of the NLST, except extending the upper age limit to 80 years (ie, ages 55–80 years, smoked at least 30 pack-years, and no more than 15 years since quitting) (3). In 2014, research suggested that basing eligibility on individualized risk calculators could make screening more effective and efficient because risk calculators can finely account for all risk factors to more precisely estimate the benefits and harms of screening for individuals (4–6). However, the USPSTF instead called for "more research to improve risk assessment tools" (3). Of note, researchers in Canada, the United Kingdom, and Europe have already proposed that screening eligibility be based on risk calculators (7,8).

Currently, the USPSTF is reconsidering whether to recommend use of risk calculators to decide on screening eligibility (9). To inform the USPSTF, CISNET researchers such as ten Haaf et al. (10) have now provided microsimulation results by simulating lifetimes based on the 1950 and 1960 US birth cohorts. In this issue of the Journal, they calculated risk according to three validated risk models (Bach [11]; $PLCO_{M2012}$ [6]; Lung Cancer Death Risk Assessment Tool [LCDRAT] [12]; limited to information on age, sex, and smoking history only), identified the earliest age at which each simulated individual exceeded a risk threshold to initiate screening, and then calculated the reduction in lifetime lung cancer deaths and gain in life-years. They conclude that, fixing the number of population lifetime screens to be similar to those under current USPSTF guidelines, risk-based screening could save more lives than current USPSTF guidelines but not appreciably increase the number of life-years gained in the population.

The approach used by ten Haaf et al. (10) differs from other approaches to modeling the effect of risk-based screening in one key consideration: Whereas ten Haaf et al. simulates a population of people from birth to death, other approaches start with a real-life current population of people who have ever smoked (ie, "ever-smokers"; either from a study [5,6,13,14] or from the US population [12,15]) and then either estimates short-term outcomes or simulates the rest of their lifetimes to death. The ten Haaf et al. (10) approach is most relevant for a well-screened population, where people enter screening at the very first age when they become eligible. For risk-based screening, this occurs when they barely exceed a risk threshold. However, because less than 10% of those eligible in the United States have been screened (16), the United States is essentially an unscreened population. Therefore, introducing risk-based screening today would screen more individuals at risks considerably higher than the risk threshold. Because the number of lives saved is proportional to the average risk at the time of entering screening (5), the number of deaths averted by screening is higher when beginning screening in an unscreened population than when continuing screening in a well-screened population. Thus, the ten Haaf et al. (10) approach will probably underestimate the number of lives saved by starting risk-based

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screening in unscreened populations like the US population. However, these authors' (10) findings are a valuable reminder of the limits of the continued benefits of screening in a well-screened population.

An important point raised by ten Haaf et al. (10) is the very different 6-year risk thresholds required by the three risk models for similar numbers of lifetime screens and similarly higher numbers of lives saved vs USPSTF guidelines: 2.8% (Bach), 1.7% ($PLCO_{M2012}$), 1.7% (LCDRAT) (note that LCDRAT is lung cancer death risk, whereas Bach/$PLCO_{M2012}$ is lung cancer incidence risk). Using these risk thresholds, according to 2015 NHIS data, we calculated that the number of US ever-smokers ages 55–80 years and eligible for screening are: 7.7 million (Bach), 9.8 million ($PLCO_{M2012}$), and 7.7 million (LCDRAT), in comparison with 8.0 million (USPSTF). If these thresholds were used today to select ever-smokers for screening in the United States, it is likely that the $PLCO_{M2012}$ model would screen millions more people and thus perform very differently compared with the Bach and LCDRAT models. Previous empirical modeling has suggested that a 2.19% $PLCO_{M2012}$ risk threshold would screen the same number of US ever-smokers as USPSTF guidelines, while averting more lung cancer deaths (17). In contrast, ten Haaf et al. (10) found that a 2.2% threshold for $PLCO_{M2012}$ would also screen similar numbers of US ever-smokers (with fewer lifetime screens) as would USPSTF guidelines, but would not avert more lung cancer deaths. In our opinion, the difference may be due to prior analyses considering unscreened populations, whereas ten Haaf et al. (10) presume a well-screened population.

The most important message of ten Haaf et al. (10) is that selecting people at highest risk does not optimize the number of life-years gained in a population, which has also been noted elsewhere (14,15). Risk-based screening tends to include older people with comorbidities, who have reduced life expectancy and reduced life gained from screening. For this legitimate reason, some medical societies have declined to endorse risk-based lung cancer screening (18). ten Haaf et al. (10) provide a novel reason for the near equivalence in life-years gained between risk-based and USPSTF approaches for a well-screened population: USPSTF starts and stops screening at much younger ages than risk-based approaches do, and thus, despite preventing fewer lung cancer deaths, the USPSTF guidelines can accrue more life-years—per life saved—than can risk-based approaches for the same number of computed tomography screens. Although the life-years gainable by risk-based screening in an unscreened population may be higher than suggested by ten Haaf et al. (10), their conceptual point is clear.

A fix-up for the risk-based approach is to require a minimum life expectancy for high-risk individuals to enter screening (15,19). ten Haaf et al. (10) suggest that requiring at least 5 years of life expectancy may greatly reduce overdiagnosis. However, this alternative does not allow medium-risk but high–life expectancy individuals to enter screening. Such individuals could live decades longer if their life were saved by screening. The ideal approach to selecting people for screening should jointly incorporate both individualized risk and individualized life expectancy to not only prevent the most deaths but also gain the most life-years in the population (20).

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