Risk models to select high risk candidates for lung cancer screening

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Lung cancer is a leading cause of cancer-related death among men and women globally and the United States (1,2). The 5-year survival for lung cancer patients has only marginally approved over the last several decades, largely attributed to lack of early detection. As such, the majority of people who are diagnosed with lung cancer will die from their disease due to the late stage at diagnosis. Early stage cancer is often curable, and so earlier detection saves lives. For decades a screening test to detect early stage lung cancer has been elusive, even among high-risk individuals. The National Lung Screening Trial (NLST) demonstrated that screening with low-dose helical computed tomography (LDCT) is associated with a 20% reduction in overall mortality among high-risk current and former smokers (3). Based on the results from the NLST, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation for annual lung cancer screening by LDCT for adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (4). Following the USPSTF recommendations, the Centers for Medicare and Medicaid (CMS) and the Affordable Care Act included lung cancer screening as an additional preventive service benefit available to Medicare recipients and under private health insurance policies, respectively (5,6).

Despite the mortality reduction benefit associated with lung cancer screening, there are many limitations of LDCT screening including high false-positive rates, detection of indeterminate pulmonary nodules (IPNs) of which only a fraction actually develop into cancer, and overdiagnosis of slow growing, indolent cancers that that may pose no threat if left untreated (3,7-11). Additionally, current inclusion guidelines from the USPSTF and CMS are derived from NLST enrollment criteria rather than precision-based methods such as risk prediction models. As such, less than 27% of Americans diagnosed with lung cancer meet the current screening entry criteria (12). A prior *post hoc* analysis (13) using data from the NLST and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) demonstrated that selection of individuals for lung cancer screening based on individual risk is superior to inclusion selection criteria using only age and pack-years smoked. Thus, to further investigate the possible benefit of risk-based lung cancer screening, Tammemagi and colleagues (14) conducted a prospective, single-arm study using the PanCan risk prediction model to enroll participants for LDCT screening for lung cancer and the results were published in the November 2017 issue of *The Lancet Oncology*. Between September 2008 and December 2010, the Pan-Canadian Early Detection of Lung Cancer (PanCan) study enrolled 2,537 individuals aged 50 to 75 years on the basis of a highly predictive lung cancer risk model. Enrolled participants received LDCT scans at baseline, 1 year, and 4 years; after a median follow-up time of 5.5 years (IQR, 3.2–6.1 years), 164 individuals were diagnosed with lung cancer for a cumulative lung cancer incidence of 0.065 (95% CI: 0.055–0.075). Of particular importance, the observed lung cancer incidence was statistically significantly 4% higher (P<0.001) than the incidence found in the NLST,

which also had three scans (at baseline, 1 year, and 2 years) with 6.5 years of follow-up. Importantly, the PanCan study also study found a significant stage shift with 77% of the lung cancers diagnosed as early stage (stage I or II) compared to 57% in the NLST (P<0.001).

Certainly there are some limitations that can be noted about the PanCan Study. The optimal study design would have been a randomized clinical trial comparing the incidence rates of risk-model enrollment versus NLST inclusion criteria rather than comparing the results of their single-arm trial to the results of prior publish trials (i.e., the NLST) and registry data. Additionally, the PanCan study is a somewhat modest sample size especially when compared to other successful lung cancer screening trials such as the NLST (3) and Dutch-Belgian Lung Cancer Screening trial (NELSON) (15). Despite these modest limitations, the findings from the PanCan study are provocative and timely especially in light of the Cancer Moonshot Initiative and its Blue Ribbon Panel Report on Precision Prevention and Early Detection (16,17) which proposes an initiative to focus research to identify individuals with the highest cancer risk. Clearly, Tammemagi and colleagues' (14) use of a low-cost, non-invasive, and validated risk assessment tool to identify high-risk individuals has many obvious advantages compared to using biomarkers for risk assessment. Most notably, the predictors in the PanCan risk model are often readily available in medical records and, if not available, they are easy to collect which include: age, sex, smoking history, family history of lung cancer, presence of chronic obstructive pulmonary disease (COPD), educational level, and body mass index. Although self-reported history of COPD was one of the predictors, of particular importance was their finding that impaired lung function [forced expiratory volume in 1 second (FEV_1)] was associated with a 4.59-fold increased risk for lung cancer. In fact, Mueller and colleagues (18) recently reported that including lung function data in a risk prediction improved predictive ability and such data may improve eligibility criteria for lung cancer screening programs. Given the necessity to perform spirometry to measure lung function, additional study will be needed to assess the cost-benefit as well as the magnitude of improvement in risk prediction to determine whether such predictors are needed.

Despite the simplicity and efficacy of using a risk model for lung cancer screening eligibility, there are still likely barriers and reluctance for adoption. First, currently lung cancer screening uptake is largely very low in the United States. Despite the life-saving benefit of early detection, only a fraction of high-risk individuals, based on current inclusion criteria are getting screened and primary care provider referral is very low (19-21). However, by identifying and targeting only those individuals who are at the very highest risk could potentially improve lung cancer screening. Additional study will be needed to understanding barriers and perspectives on risk model eligibility across the continuum of clinical care, to determine if cost concerns remain as a perceived barrier to screening, and to better understand how potentially changing risk/benefit ratios impacts perspectives on screening among the highest risk individuals. Next, over the last several decades identifying high-risk individuals using risk prediction models has received increasing interest and has resulted in nearly 20 different published lung risk cancer models [reviewed in (22)]. As such, the lung cancer screening community may be reluctant and apprehensive to choose a "winner". The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Lung Cancer Screening (23) includes language recognizing "*there are individuals who would not have met the NLST criteria but are at similar risk to the NLST cohort and recommends lung cancer screening for these individuals. However, substantial uncertainty exists about the true benefits and harms of screening these individuals.*" As such, the NCCN Lung Cancer Screening Guidelines have considered it reasonable to consider using a lung cancer risk calculator (https://brocku.ca/lung-cancer-risk-calculator) to assist in quantifying risk for individuals in this group. Based on the most recent findings from Tammemagi and colleagues (14), an additional consideration is warranted on the clinical guidelines for implementation of risk-based modeling in lung cancer screening.

In the United States, smoking rates have steadily declined since the 1960s (17). Today, nearly 18% of adults in the United States currently smoke cigarettes (18). Even after smoking cessation is successfully accomplished, former smokers remain at significant risk of developing lung cancer. Lung cancer screening is second only to primary prevention (smoking prevention and cessation) for mitigating lung-cancer mortality, and currently is the only option for those who have already quit smoking and are at high risk for disease. As such, lung cancer will likely remain a major public health burden for decades to come, and improvements in risk assessment and early detection will be remain relevant and important to improve patient outcomes of this disease.

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Footnote

Conflicts of Interest: Dr. Schabath is a Panel Member of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Lung Cancer Screening.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. American Cancer Society. Global Cancer Facts & Figures 3rd Edition. Atlanta: American Cancer Society, 2015.
3. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. US. Preventive Services Task Force. Screening for lung cancer. Available online: http://www.uspreventiveservicestaskforce.org/uspstf/uspslung.htm
5. The Centers for Medicare and Medicaid. Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). Available online: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274
6. HealthCare.gov. Preventive care benefits for adults. Available online: https://www.healthcare.gov/preventive-care-adults/
7. Patz EF, Jr., Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014;174:269-74.
8. Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer. Cochrane Database Syst Rev 2013:CD001991.
9. Thalanayar PM, Altintas N, Weissfeld JL, et al. Indolent, Potentially Inconsequential Lung Cancers in the Pittsburgh Lung Screening Study. Ann Am Thorac Soc 2015;12:1193-6.
10. Pinsky PF. Assessing the benefits and harms of low-dose computed tomography screening for lung cancer. Lung Cancer Manag 2014;3:491-8.
11. Massion PP, Walker RC. Indeterminate pulmonary nodules: risk for having or for developing lung cancer? Cancer Prev Res (Phila) 2014;7:1173-8.
12. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen 2012;19:154-6.
13. Ten Haaf K, Jeon J, Tammemagi MC, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 2017;14:e1002277.
14. Tammemagi MC, Schmidt H, Martel S, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. Lancet Oncol 2017;18:1523-31.
15. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax 2017;72:48-56.
16. The National Cancer Instituute. Cancer Moonshot[SM]. Available online: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative
17. The National Cancer Institute. Cancer Moonshot[SM] Blue Ribbon Panel: Precision Prevention and Early Detection Working Group Report. Available online: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/prevention-screening-working-group-report.pdf
18. Muller DC, Johansson M, Brennan P. Lung Cancer Risk Prediction Model Incorporating Lung Function: Development and Validation in the UK Biobank Prospective Cohort Study. J Clin Oncol 2017;35:861-9.
19. Jemal A, Fedewa SA. Lung Cancer Screening With Low-Dose Computed Tomography in the United States-2010 to 2015. JAMA Oncol 2017;3:1278-81.
20. Barton MK. Integration of lung cancer screening into practice is lacking. CA Cancer J Clin 2015;65:255-6.
21. The ASCO Post. The Ongoing Challenges of Lung Cancer Screening. Available online: http://www.ascopost.com/issues/may-25-2017/the-ongoing-challenges-of-lung-cancer-screening/. 2017.
22. Tammemagi MC. Application of risk prediction models to lung cancer screening: a review. J Thorac Imaging 2015;30:88-100.
23. Wood DE, Kazerooni E, Baum SL, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Lung Cancer Screening, Version 2.2018. J Natl Compr Canc Netw Available online: https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf

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