ORIGINAL ARTICLE

Selection Criteria for Lung-Cancer Screening

Martin C. Tammemägi, Ph.D., Hormuzd A. Katki, Ph.D., William G. Hocking, M.D., Timothy R. Church, Ph.D., Neil Caporaso, M.D., Paul A. Kvale, M.D., Anil K. Chaturvedi, Ph.D., Gerard A. Silvestri, M.D., Tom L. Riley, B.Sc., John Commins, B.Sc., and Christine D. Berg, M.D.

ABSTRACT

BACKGROUND

The National Lung Screening Trial (NLST) used risk factors for lung cancer (e.g., ≥30 pack-years of smoking and <15 years since quitting) as selection criteria for lung-cancer screening. Use of an accurate model that incorporates additional risk factors to select persons for screening may identify more persons who have lung cancer or in whom lung cancer will develop.

METHODS

We modified the 2011 lung-cancer risk-prediction model from our Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to ensure applicability to NLST data; risk was the probability of a diagnosis of lung cancer during the 6-year study period. We developed and validated the model ($PLCO_{M2012}$) with data from the 80,375 persons in the PLCO control and intervention groups who had ever smoked. Discrimination (area under the receiver-operating-characteristic curve [AUC]) and calibration were assessed. In the validation data set, 14,144 of 37,332 persons (37.9%) met NLST criteria. For comparison, 14,144 highest-risk persons were considered positive (eligible for screening) according to $PLCO_{M2012}$ criteria. We compared the accuracy of $PLCO_{M2012}$ criteria with NLST criteria to detect lung cancer. Cox models were used to evaluate whether the reduction in mortality among 53,202 persons undergoing low-dose computed tomographic screening in the NLST differed according to risk.

RESULTS

The AUC was 0.803 in the development data set and 0.797 in the validation data set. As compared with NLST criteria, $PLCO_{M2012}$ criteria had improved sensitivity (83.0% vs. 71.1%, P<0.001) and positive predictive value (4.0% vs. 3.4%, P=0.01), without loss of specificity (62.9% and. 62.7%, respectively; P=0.54); 41.3% fewer lung cancers were missed. The NLST screening effect did not vary according to $PLCO_{M2012}$ risk (P=0.61 for interaction).

CONCLUSIONS

The use of the $PLCO_{M2012}$ model was more sensitive than the NLST criteria for lung-cancer detection.

From the Department of Community Health Sciences, Brock University, St. Catharines, ON, Canada (M.C.T.); the Division of Cancer Epidemiology and Genetics (H.A.K., N.C., A.K.C.) and the Early Detection Research Group, Division of Cancer Prevention (C.D.B.), National Cancer Institute, National Institutes of Health, and Information Management Services (T.L.R., J.C.) — all in Rockville, MD; Marshfield Clinic Research Foundation, Marshfield, WI (W.G.H.); the School of Public Health, University of Minnesota, Minneapolis (T.R.C.); Henry Ford Health System, Detroit (P.A.K.); and Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston (G.A.S.). Address reprint requests to Dr. Tammemägi at the Department of Community Health Sciences, Walker Complex South, Rm. 306, Brock University, 500 Glenridge Ave., St. Catharines, ON L2S 3A1, Canada, or at martin.tammemagi@brocku.ca.

This article was updated on July 3, 2013, at NEJM.org.

N Engl J Med 2013;368:728-36.
DOI: 10.1056/NEJMoa1211776

The National Lung Screening Trial (NLST) showed that lung-cancer screening with the use of low-dose computed tomography (CT) resulted in a 20% reduction in mortality from lung cancer.[1] Some organizations now recommend adoption of lung-cancer screening in clinical practice for high-risk persons if high-quality imaging, diagnostic methods, and treatment are available.[2-4] Most of these recommendations identify persons to be screened by applying the NLST criteria, which include an age between 55 and 74 years, a history of smoking of at least 30 pack-years, a period of less than 15 years since cessation of smoking, or some variant of these criteria. These selection criteria were intended to increase the yield of lung cancers, but they exclude many known risk factors for lung cancer, and with dichotomization of continuous data, much valuable information is not included.[5] Thus, NLST enrollment criteria may not identify substantial numbers of persons who will receive a diagnosis of lung cancer, and they may not sensitively select lung-cancer cases in screening samples. Applying an accurate lung-cancer risk-prediction model to a population can identify persons at highest risk; screening them is expected to increase the number of lung cancers identified per given sample size or reduce the number of persons needed to be screened per fixed number of lung cancers detected.

We previously developed and validated a lung-cancer risk-prediction model involving former and current smokers in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial control and intervention groups.[6] Model predictors included age, level of education, body-mass index (BMI), family history of lung cancer, chronic obstructive pulmonary disease (COPD), chest radiography in the previous 3 years, smoking status (current smoker vs. former smoker), history of cigarette smoking in pack-years, duration of smoking, and quit time (the number of years since the person quit smoking). This model has high predictive discrimination measured with the use of the area under the receiver-operating-characteristic curve (AUC), but it can be cumbersome to apply because it uses complicated modeling procedures (i.e., restricted cubic splines) and may benefit from the inclusion of additional predictors. In the PLCO model, risks are based on a median follow-up of 9.2 years, which exceeds the follow-up in the NLST and makes estimates inaccurate when applied to the NLST.

The aims of the current study were to modify and update our lung-cancer model for current and former smokers to make it directly applicable to NLST data. We also aimed to evaluate the extent to which selection of participants with the use of model-estimated high risk is more efficient than NLST criteria. We used each method to select PLCO intervention-group participants and determined the classification accuracies for selecting persons who receive a diagnosis of lung cancer in 6 years of follow-up.

Methods

Study Design

The PLCO and NLST study designs and results have been described previously,[1,7-11] and the designs and methods are summarized in Table 1. In both trials, approvals were obtained from institutional review boards at all study centers, and written informed consent was obtained from all participants. The current study involved 73,618 smokers in the PLCO study and 51,033 NLST participants for whom epidemiologic data were available. All histologically confirmed lung cancers that were diagnosed from study entry through 6 years of follow-up were included. Data on predictor variables were collected with the use of epidemiologic questionnaires administered at study entry.

Statistical Analysis

We developed a modified logistic-regression model for lung-cancer prediction in the PLCO control group of smokers. This model was referred to as $PLCO_{M2012}$ to distinguish it from its predecessor, $PLCO_{M2011}$. We validated the model in the PLCO intervention group of smokers, NLST participants, and in the PLCO intervention group stratified according to whether or not they met NLST criteria. In all data sets, follow-up was truncated at 6 years to make comparisons uniform between groups. Predictor variables considered for entry into the model included risk factors for lung cancer recognized in the literature and $PLCO_{M2011}$.[6,15-19] Model development was guided by predictive performance and was not limited to predictors with a P value of less than 0.05. Selected interactions thought to be credible a priori were evaluated, including sex–race or ethnic group and sex–smoking interactions. All interactions were found to be nonsignificant and are not discussed further. Nonlinear associations between continuous variables and lung cancer were evaluated with the

Table 1. Designs and Methods in the PLCO Cancer Screening Trial and the NLST.*

Variable	PLCO Cancer Screening Trial	NLST
Intervention group	Posteroanterior chest radiography in 77,445 persons	Low-dose CT in 26,722 persons
Control group	Regular care in 77,456 persons	Posteroanterior chest radiography in 26,732 persons
Total no. of participants	154,901	53,454
No. of study sites	10 centers	33 centers
Eligibility criteria		
Age	55–74 yr	55–74 yr
Smoking status	Any	≥30 pack-yr; quit time <15 yr before enrollment
Exclusion criteria	History of prostate, lung, colorectal, or ovarian cancer; current cancer treatment; removal of one lung	Previous diagnosis of lung cancer; chest radiography within 1.5 yr before enrollment; hemoptysis, unexplained weight loss of >6.8 kg (15 lb) in the preceding yr
Enrollment period	November 1993–July 2001	August 2002–April 2004
Screening period	November 1993–November 2004	August 2002–September 2007
Follow-up	To year 13 or December 31, 2009, whichever was earlier	To December 31, 2009
Screening schedule	Four screenings: at baseline, year 1, year 2, and year 3 (year 3 screening not given to persons who never smoked after April 1995)	Three screenings: at baseline, year 1, and year 2
Criteria for positivity (abnormal finding that raises clinical suspicion of lung cancer)	Nodule or mass, infiltrate, pleural mass, noncalcified hilar or mediastinal lymphadenopathy, or major atelectasis[12]	Noncalcified nodule >4 mm detected on CT, any noncalcified nodule or mass detected on chest radiography
Lung-cancer classification	ICD-O-2[13]	ICD-O-3[14]
References	Prorok et al.,[7] Oken et al.,[8] and Oken et al.[9]	Aberle et al.,[1] Aberle et al.,[10] and Aberle et al.[11]

* CT denotes computed tomography, ICD-O-2 *International Classification of Diseases for Oncology, 2nd Edition*, ICD-O-3 *International Classification of Diseases for Oncology, 3rd Edition,* NLST National Lung Screening Trial, and PLCO Prostate, Lung, Colorectal, and Ovarian.

use of multivariable fractional polynomials.[20] We evaluated modeling assumptions and assessed model fit by graphically plotting residuals against model parameter values.

The ability of the models to discriminate between lung-cancer cases and noncases was evaluated according to the AUC in the validation data set. Model calibration (how well predicted probabilities corresponded to observed probabilities) was assessed by plotting a smoothed curved line with a locally weighted scatterplot smoothing (LOWESS) plot showing the relationship between observed and predicted probabilities of lung cancer. The mean absolute differences in observed and predicted probabilities for each decile of predicted risk were assessed. As summary statistics, the median and 90th-percentile absolute differences between observed and predicted values are presented.[21] Improvement in classification of cases, noncases, and cases and noncases combined from the inclusion of selected variables in models was analyzed with the use of net reclassification improvement[22] with the following levels of 6-year risk: low, less than 1.0%; intermediate, 1.0% to less than 2.0%; and high, 2.0% or more.

Next, we applied the NLST smoking criteria (≥30 pack-years of smoking and <15 years since cessation) to the PLCO intervention-group smokers; this provided the number of persons who met the NLST criteria. We selected a $PLCO_{M2012}$ risk cutoff point so that the number of persons above this point was exactly the same as the number of persons who met the NLST criteria. This provided comparison samples of equal size, which were positive according to each criterion. The method that selected the largest proportion of diagnosed lung cancers in these samples would be the most efficient one to use in screening programs. We compared the sensitivity, specificity, and predictive values of both sets of criteria for selecting lung cancers. Confidence intervals for proportions were prepared with the use of the binomial exact method.[23]

Table 2. Modified Logistic-Regression Prediction Model ($PLCO_{M2012}$) of Cancer Risk for 36,286 Control Participants Who Had Ever Smoked.*

Variable	Odds Ratio (95% CI)	P Value	Beta Coefficient
Age, per 1–yr increase†	1.081 (1.057–1.105)	<0.001	0.0778868
Race or ethnic group‡			
White	1.000		Reference group
Black	1.484 (1.083–2.033)	0.01	0.3944778
Hispanic	0.475 (0.195–1.160)	0.10	–0.7434744
Asian	0.627 (0.332–1.185)	0.15	–0.466585
American Indian or Alaskan Native	1		0
Native Hawaiian or Pacific Islander	2.793 (0.992–7.862)	0.05	1.027152
Education, per increase of 1 level†§	0.922 (0.874–0.972)	0.003	–0.0812744
Body-mass index, per 1-unit increase†	0.973 (0.955–0.991)	0.003	–0.0274194
Chronic obstructive pulmonary disease (yes vs. no)	1.427 (1.162–1.751)	0.001	0.3553063
Personal history of cancer (yes vs. no)	1.582 (1.172–2.128)	0.003	0.4589971
Family history of lung cancer (yes vs. no)	1.799 (1.471–2.200)	<0.001	0.587185
Smoking status (current vs. former)	1.297 (1.047–1.605)	0.02	0.2597431
Smoking intensity¶			–1.822606
Duration of smoking, per 1-yr increase†	1.032 (1.014–1.051)	0.001	0.0317321
Smoking quit time, per 1-yr increase†	0.970 (0.950–0.990)	0.003	–0.0308572
Model constant			–4.532506

* To calculate the 6-year probability of lung cancer in an individual person with the use of categorical variables, multiply the variable or the level beta coefficient of the variable by 1 if the factor is present and by 0 if it is absent. For continuous variables other than smoking intensity, subtract the centering value from the person's value and multiply the difference by the beta coefficient of the variable. For smoking intensity, calculate the contribution of the variable to the model by dividing by 10, exponentiating by the power –1, centering by subtracting 0.4021541613, and multiplying this number by the beta coefficient of the variable. Add together all the previously calculated beta-coefficient products and the model constant. This sum is called the model logit. To obtain the person's 6-year lung-cancer probability, calculate $e^{logit}/(1+e^{logit})$. CI denotes confidence interval.

† Age was centered on 62 years, education was centered on level 4, body-mass index was centered on 27, duration of smoking was centered on 27 years, and smoking quit time was centered on 10 years.

‡ Race or ethnic group was self-reported.

§ Education was measured in six ordinal levels: less than high-school graduate (level 1), high-school graduate (level 2), some training after high school (level 3), some college (level 4), college graduate (level 5), and postgraduate or professional degree (level 6).

¶ Smoking intensity (the average number of cigarettes smoked per day) had a nonlinear association with lung cancer, and this variable was transformed. For this reason, the odds ratio is not directly interpretable in a meaningful fashion.

Finally, to see whether the reduction in mortality associated with low-dose CT screening in the NLST varied according to the risk of lung cancer, we prepared a Cox regression model using NLST data with a screening intervention–$PLCO_{M2012}$ risk interaction. The significance of this multiplicative interaction term was evaluated with the use of the Wald statistic. We present Cox model hazard ratios for the screening-intervention variable stratified according to quartiles of $PLCO_{M2012}$ risk.

With regard to descriptive statistics, distributions of study variables according to lung-cancer status were compared with the use of Fisher's exact test for categorical variables, the t-test for continuous variables, and the nonparametric test for ordinal variables. All statistics and figures were prepared with the use of Stata software, version MP12.1 (Stata). All hypothesis testing used an alpha-error cutoff point of 0.05.

RESULTS

STUDY POPULATIONS

Distributions of predictor variables in 80,375 smokers in the PLCO control and intervention groups, in combined groups of the NLST (53,202 persons), and in the PLCO intervention group of

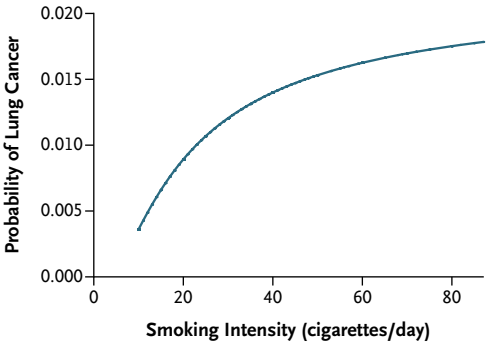

Figure 1. Nonlinear Relationship between Smoking Intensity (Average Number of Cigarettes Smoked per Day) and Lung-Cancer Risk.

Probabilities were calculated on the basis of the following variables: an age of 62 years, white race or ethnic group, some college education, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27, no chronic obstructive pulmonary disease, no personal history of cancer, no family history of lung cancer, status as a former smoker, smoking history of 27 years, and cessation of smoking 10 years before enrollment.

persons who met NLST smoking criteria (15,099 persons) are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Because the goal of the current study was not to reevaluate NLST intervention effects and because the distribution of participant characteristics according to NLST study groups has already been published,[1,11,24] we used pooled statistics to provide an overall description of NLST participants as compared with PLCO participants. Table S1 in the Supplementary Appendix shows incidence rates of lung cancer and mean probabilities of lung cancer in former and current smokers. The higher incidence observed among NLST former smokers resulted from the exclusion of former smokers with histories of light smoking (<30 pack-years).

MODIFIED PLCO LUNG-CANCER RISK-PREDICTION MODEL ($PLCO_{M2012}$)

In $PLCO_{M2012}$ (Table 2), the risk of lung cancer increased with age, black vs. white race, lower socioeconomic status (determined according to the level of education), lower BMI, self-reported history of COPD, personal history of cancer, family history of lung cancer, current smoking, increased smoking intensity (the average number of cigarettes smoked per day) and duration, and, in former smokers, shorter time since quitting. In multivariable modeling, smoking intensity had a significant nonlinear association with lung cancer ($P<0.001$ for nonlinearity) (Fig. 1 and Table 2). The increase in risk became smaller as smoking intensity increased. Inclusion of smoking intensity in the model as a nonlinear variable rather than a linear variable led to an overall net reclassification improvement in the PLCO control group of 2.1% ($P=0.02$) and an increase in the AUC from 0.789 to 0.803 ($P=0.04$). Inclusion of status with respect to a personal history of cancer and race or ethnic group, which were excluded from $PLCO_{M2011}$, led to an overall net reclassification improvement of 0.9% ($P=0.16$) and improvement increase in the AUC from 0.799 to 0.803 ($P=0.05$). These incremental improvements in prediction seem modest, but it is difficult to achieve large gains in prediction when adding new predictors to a strong base model.[25] The results of net-reclassification-improvement analyses are included in Table S2 in the Supplementary Appendix.

In $PLCO_{M2012}$, the AUC for smokers in the PLCO control group (the development sample) was 0.803 (95% confidence interval [CI], 0.782 to 0.813), and the AUC for smokers in the PLCO intervention group (the validation sample) was 0.797 (95% CI, 0.782 to 0.813) (Table 3, and Fig. S1 in the Supplementary Appendix). In contrast, when the NLST criteria were applied, the AUC was 0.689 (95% CI, 0.673 to 0.795) for smokers in the PLCO control group and 0.670 (95% CI, 0.653 to 0.686) for those in the intervention group. In $PLCO_{M2012}$, the AUC for the NLST participants was 0.701 (95% CI, 0.689 to 0.712), and for PLCO intervention participants who met the NLST criteria, it was 0.710 (95% CI, 0.689 to 0.732). The latter two AUCs were lower than those observed in the PLCO development and validation data sets because of a higher concentration of high-risk persons (persons who had never smoked and light smokers were excluded). High discrimination is easier to attain in data that are heterogeneous with regard to risk.

$PLCO_{M2012}$ calibration assessment in the PLCO intervention-group smokers (Table 3) showed that the median and 90th percentile absolute differences between observed and predicted risk probabilities were 0.009 and 0.042, respectively. That is, the difference between observed and pre-

dicted probabilities of lung-cancer risk was less than 0.010 in half the validation sample and less than 0.043 in 90% of the sample. The mean absolute differences between observed and predicted lung-cancer risk in increasing deciles of $PLCO_{M2012}$ risk are shown in Figure S2 in the Supplementary Appendix. In each of the first five deciles of risk, the mean absolute differences in risks were 0.015 or less, and in the first nine deciles of risk, the mean absolute differences in risks were 0.043 or less.

For comparative purposes, we prepared a Cox survival model with the same predictors as in the logistic $PLCO_{M2012}$ model. The effect estimates (hazard ratios and odds ratios), standard errors, and predictive performances were similar in the two models (Table S3 in the Supplementary Appendix compares beta coefficients between the models). Because the logistic model is simpler, we describe it here. A spreadsheet calculator is available online (www.brocku.ca/cancerpredictionresearch); it calculates lung-cancer risk according to the $PLCO_{M2012}$ model, given a person's predictor levels.

SELECTION FOR LUNG SCREENING WITH THE RISK MODEL VERSUS NLST CRITERIA

When the NLST criteria were applied to the PLCO intervention group, 14,144 of 37,332 smokers (37.9%) were eligible for screening. For an equal number of persons with the use of the $PLCO_{M2012}$ criteria, persons with a lung-cancer risk higher than 1.3455% were eligible. The distributions of true and false positive and negative results according to NLST and $PLCO_{M2012}$ criteria are shown in Table 4. In the comparison of NLST with $PLCO_{M2012}$ criteria for selection of persons who received a diagnosis of lung cancer, the sensitivities were 71.1% versus 83.0% ($P<0.001$), the specificities were 62.7% versus 62.9% ($P=0.54$), and the positive predictive values were 3.4% versus 4.0% ($P=0.01$). Of the persons who were excluded from screening according to NLST and $PLCO_{M2012}$ criteria, lung cancer developed in 0.85% and 0.50%, respectively ($P<0.001$). All accuracy measurements favored the $PLCO_{M2012}$ risk model. Overall, the model identified 81 more of the 678 lung cancers (11.9%) (95% CI, 9.6 to 14.6) than did the NLST criteria (41.3% fewer lung cancers were not detected; 115 vs.196).

On the basis of the performance of the model in the PLCO control smokers, 90% of persons who received a diagnosis of cancer within 6 years would be selected for screening with the use of the $PLCO_{M2012}$ risk probability of 0.00948 or higher (specificity, 52.0%; positive predictive value, 3.2%), and 48.7% of smokers would have to be screened. To include 80% of lung cancers, a $PLCO_{M2012}$ risk probability of 0.016082 or higher would be used (specificity, 67.3%; positive predictive value, 4.1%) and the proportion of smokers to be screened would be 33.6%.

Table 3. Predictive Performance of the $PLCO_{M2012}$ Model.

Statistic	Value
AUC for discrimination in 36,286 PLCO control smokers (95% CI)	0.803 (0.782–0.813)
AUC in external-validation data set (95% CI)	
In 37,332 PLCO intervention-group smokers	0.797 (0.782–0.813)
In 51,033 NLST participants	0.701 (0.689–0.712)
In 14,144 PLCO intervention-group smokers who met NLST criteria	0.710 (0.689–0.732)
In 23,188 PLCO intervention-group smokers who did not meet NLST criteria	0.780 (0.744–0.811)
Calibration in PLCO intervention-group smokers	
Median absolute error	0.009
90th percentile absolute error	0.042

MODIFICATION OF NLST SCREENING EFFECT ACCORDING TO LUNG-CANCER RISK

In Cox models with the use of NLST data, the protective effect of low-dose CT screening did not differ according to $PLCO_{M2012}$ lung-cancer risk ($P=0.61$ for interaction). We divided $PLCO_{M2012}$ risk into four roughly equal groups of increasing risk and evaluated the Cox model hazard ratios for low-dose CT versus chest radiography. The hazard ratios were 0.86 (95% CI, 0.50 to 1.48), 0.71 (95% CI, 0.49 to 1.04), 0.70 (95% CI, 0.53 to 0.91), and 0.88 (95% CI, 0.73 to 1.06), respectively. At all four levels of risk, the screening effect was protective. Random variation may explain differences in hazard ratios according to risk quartiles.

DISCUSSION

In our original $PLCO_{M2011}$ risk-prediction model, the AUC for smokers in the control group (the development sample) was 0.809 and the AUC for the intervention group (the validation sample) was

Table 4. Accuracy of Lung-Cancer Classification According to Alternative Criteria in the PLCO Intervention-Group Smokers.*

Criteria†	Participants with Lung Cancer (N=678)	Participants without Lung Cancer (N=36,654)	Total Participants (N=37,332)	Predictive Value
NLST				
Criteria positive	482 TP (3.4%)	13,662 FP (96.6%)	14,144	PPV, 3.4%
Criteria negative	196 FN (0.8%)	22,992 TN (99.2%)	23,188	NPV, 99.2%
Sensitivity	71.1%			
Specificity		62.7%		
$PLCO_{M2012}$ ‡				
Criteria positive	563 TP (4.0%)	13,581 FP (96%)	14,144	PPV, 4.0%
Criteria negative	115 FN (0.5%)	23,073 TN (99.5%)	23,188	NPV, 99.5%
Sensitivity	83.0%			
Specificity		62.9%		

* FN denotes false negative, FP false positive, NPV negative predictive value, PPV positive predictive value, TN true negative, and TP true positive.
† NLST criteria for study entry included a history of cigarette smoking of at least 30 pack-years and, for former smokers, cessation within the previous 15 years.
‡ According to the $PLCO_{M2012}$ criteria, positivity was defined as a probability of lung cancer that was greater than 1.3455% over a period of 6 years.

0.784. These values indicate high and consistent predictive discrimination. With our modified model, $PLCO_{M2012}$, the AUCs were similar, at 0.803 and 0.797, respectively. The AUCs in the validation data suggest that predictive discrimination with the $PLCO_{M2012}$ was slightly improved. A predictive model with an AUC in this range may be of value in providing individual-level information and in population-level screening programs.

The $PLCO_{M2012}$ was modified from our previous model. In the current analysis, follow-up was truncated at 6 years so that $PLCO_{M2012}$ data could be evaluated in comparison with NLST, in which complete follow-up was limited to this period. The predictor, radiography in the previous 3 years, was excluded from $PLCO_{M2012}$. Although this variable was significantly associated with lung cancer, its inclusion did not lead to an increase in the AUC. The variables "race or ethnic group" and "status with respect to a personal history of cancer" were added to $PLCO_{M2012}$. These additions are consistent with findings of other studies[17,19,26] and modestly but significantly improved prediction as measured according to the AUC, net reclassification improvement, or both. A nonlinear relationship between the predictor and lung cancer was described with the use of multivariable fractional polynomials. This approach allowed straightforward calculation of risks and made implementation of the model easy. In $PLCO_{M2011}$, smoking predictors included smoking status, duration of smoking, history of smoking in pack-years, and time since the person quit smoking. In $PLCO_{M2012}$, smoking predictors included smoking status, duration of smoking, smoking intensity, and quit time (pack-years were not included). The smoking variables can be converted from one to the other, and it is usual for different combinations of related predictors to have similar predictive abilities. Our PLCO models have advantages over previously published models, which have been described elsewhere.[6]

$PLCO_{M2012}$ excluded persons who had never smoked. Additional unique predictors and models are required for prediction of lung-cancer risk among persons who have never smoked, and such models have not been developed. Generally, lung-cancer risk among persons who have never smoked is so low that low-dose CT screening of such persons is not currently warranted. In both the PLCO and the NLST, an age between 55 and 74 years was an entry criterion. Therefore, the predictive performance of the $PLCO_{M2012}$ outside this age range is uncertain, although most lung cancers occur in persons in this age range. The socioeconomic status of the PLCO study population was

higher than that of the general population.[27] Although this might theoretically limit generalizability, because most of the predictors appear to have a biologic relationship with lung cancer that is independent of socioeconomic status, the model may still perform well. The $PLCO_{M2012}$ should be evaluated in different populations and clinical and public health settings in well-designed prospective studies. In the future, additional predictors, such as pulmonary function[28] and genetic or biomarker-based predictors, may lead to further enhancement of lung-cancer prediction.

Detailed calculations of sensitivity, specificity, and predictive values for screening low-dose CT and chest radiography were not presented in the final reports of the NLST[1] or PLCO.[9] However, the positive predictive value of low-dose CT screening in the NLST (computed from reported data) was 3.6%[1] and the positive predictive value of baseline chest radiographic screening in the PLCO was 2.0%.[29] The positive predictive value for the $PLCO_{M2012}$ (4.0%) compares favorably.

The wide gap in the ability to predict lung cancers between the NLST and $PLCO_{M2012}$ criteria should translate into more efficient selection for screening (a higher number of cancers detected per number of persons screened), greater cost-effectiveness, and additional lives saved from low-dose CT screening. Among 37,332 smokers in the PLCO intervention group, the $PLCO_{M2012}$ selected 81 more persons for screening who received a diagnosis of lung cancer in follow-up than did the NLST criteria. If one assumes a 15% rate of overdiagnosis, then 69 of these persons can be considered to have "true" life-threatening lung cancer. If the 5-year survival rate is 15%, the expected number of deaths among persons who did not undergo screening would be 59. If the mortality reduction is 20%, as observed in the NLST, then in this cohort, 12 additional deaths from lung cancer would have been avoided if selection for screening had been based on $PLCO_{M2012}$ criteria.

In conclusion, the $PLCO_{M2012}$ predicted the 6-year risk of lung cancer with high accuracy and was more efficient at identifying persons for lung-cancer screening, as compared with the NLST criteria. Because the mortality reduction from CT screening effectiveness did not vary according to lung-cancer risk, it appears that use of the $PLCO_{M2012}$ to select persons for lung-screening programs could potentially be an effective method leading to improved cost-effectiveness of screening with additional deaths from lung cancer prevented.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was supported by the National Cancer Institute (NCI), in part by contracts with the Division of Cancer Prevention and by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics. The American College of Radiology Imaging Network component of the National Lung Screening Trial (NLST) was supported by grants provided under a cooperative agreement with the Cancer Imaging Program, Division of Cancer Treatment and Diagnosis (U01-CA-80098 and U01-CA-79778). The Lung Screening Study sites of the NLST were supported by contracts with the Early Detection Research Group and Biometry Research Group, Division of Cancer Prevention (N01-CN-25514, to the University of Colorado–Denver; N01-CN-25522, to Georgetown University; N01-CN-25515, to the Pacific Health Research and Education Institute; N01-CN-25512, to the Henry Ford Health System; N01-CN-25513, to the University of Minnesota; N01-CN-25516, to Washington University in St. Louis; N01-CN-25511, to the University of Pittsburgh; N01-CN-25524, to the University of Utah; N01-CN-25518, to the Marshfield Clinic Research Foundation; N01-CN-75022, to the University of Alabama at Birmingham; N01-CN-25476, to Westat; and N02-CN-63300, to Information Management Services).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the PLCO and NLST screening-center investigators and the staff from Information Management Services and Westat. Most important, we thank the study participants for their contributions that made these studies possible.

REFERENCES

1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
2. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. J Natl Compr Canc Netw 2012;10:240-65.
3. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012;307:2418-29. [Erratum, JAMA 2012; 308:1324.]
4. Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012;144:33-8.
5. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;25:127-41.
6. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst 2011;103:1058-68.
7. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000; 21:Suppl:273S-309S.
8. Oken MM, Marcus PM, Hu P, et al. Baseline chest radiograph for lung cancer detection in the randomized Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. J Natl Cancer Inst 2005; 97:1832-9.
9. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-73.
10. Aberle DR, Berg CD, Black WC, et al.

The National Lung Screening Trial: overview and study design. Radiology 2011; 258:243-53.
11. Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized National Lung Screening Trial. J Natl Cancer Inst 2010;102:1771-9. [Erratum, J Natl Cancer Inst 2011;103: 1560.]
12. Tammemagi CM, Freedman MT, Pinsky PF, et al. Prediction of true positive lung cancers in individuals with abnormal suspicious chest radiographs: a Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial study. J Thorac Oncol 2009;4:710-21.
13. Percy CL, Van Holten V, Muir CS. International classification of diseases for oncology. 2nd ed. Geneva: World Health Organization, 1990.
14. Fritz AG. International classification of diseases for oncology: ICD-O. 3rd ed. Geneva: World Health Organization, 2000.
15. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003;95: 470-8.
16. Cronin KA, Gail MH, Zou Z, Bach PB, Virtamo J, Albanes D. Validation of a model of lung cancer risk prediction among smokers. J Natl Cancer Inst 2006; 98:637-40.
17. Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst 2007;99:715-26.
18. Spitz MR, Etzel CJ, Dong Q, et al. An expanded risk prediction model for lung cancer. Cancer Prev Res (Phila) 2008;1: 250-4.
19. Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer 2008;98:270-6.
20. Royston P, Sauerbrei W. Multivariable model-building: a pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables. Hoboken, NJ: John Wiley, 2008.
21. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.
22. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72.
23. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Stat Sci 2001;16:101-33.
24. Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. Radiology 2011; 258:243-53.
25. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. Am J Epidemiol 2012;176:473-81.
26. Etzel CJ, Kachroo S, Liu M, et al. Development and validation of a lung cancer risk prediction model for African-Americans. Cancer Prev Res (Phila) 2008; 1:255-65.
27. Pinsky PF, Miller A, Kramer BS, et al. Evidence of a healthy volunteer effect in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Am J Epidemiol 2007;165:874-81.
28. Tammemagi MC, Lam SC, McWilliams AM, Sin DD. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. Cancer Prev Res (Phila) 2011;4:552-61.
29. Hocking WG, Hu P, Oken MM, et al. Lung cancer screening in the randomized Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. J Natl Cancer Inst 2010;102:722-31.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/faq_clinical.html.