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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix Contents

Appendix Table 1. Individuals scanned and lung cancers detected in the International Lung Screening Trial study by site, with recruitment period and follow-up

Screening sites (Site principal investigator)	**Number of participants** (% of study total)	**Lung cancers detected** [detection % of scanned]	**Recruitment period:** Date of first, last baseline scans	**Follow-up** (minimum, median, maximum days)
Canada – Vancouver (Dr. Stephen Lam)	2138 (36.7%)	64 [3.0%]	25 Aug 2016, 21 Nov 2020	1, 765, 1558
Canada – Alberta (Dr. Alain Trembley)	805 (13.8%)	25 [3.11%]	17 Jun 2015, 8 Dec 2017	13, 728, 1192
Australia – Brisbane (Dr. Kwun Fong)	596 (10.2%)	17 [2.85%]	5 May 2017, 13 Dec 2019	1, 763, 1305
Australia – Perth (Dr. Annette McWilliams)	591 (10.2%)	18 [3.05%]	11 Jan 2017, 6 Dec 2019	1, 854, 1419
Australia – Melbourne 1, Royal Melbourne Hospital (Dr. Renne Manser)	407 (7.0%)	8 [1.97%]	30 May 2017, 13 Feb 2020	1, 818, 1280
Australia – Melbourne 2, Epworth (Dr. Paul Fogarty)	127 (2.2%)	2 [1.57%]	17 Apr 2018, 10 Dec 2019	10, 790, 958
Australia – Sydney (Dr. Karen Canfell)	378 (6.5%)	4 [1.06%]	9 Dec 2017, 17 Dec 2019	140, 613, 1087
Hong Kong (Dr. David Lam)	128 (2.2%)	3 [2.34%]	21 Apr 2018, 4 Jan 2020	1, 712, 954
United Kingdom (Dr. Samuel Janes)	649 (11.1%)	36 [5.55%]	2 Nov 2015, 15 Sep 2017	1, 1484, 1827
Total	5819	177 [3.04%]		

Appendix Text 1. **Discussion of Selected PLCOm2012 Predictors**

In the ILST the original PLCOm2012 was used with race/ethnicity coded in five levels: White, Black, Asian, Hispanic, and American Indian/Alaskan Native. For analysis, two sites did not provide specific race data. Of the 4,365 individuals for whom race/ethnic data were available, the distribution was 89.09% White, 7.24% East Asian, 1.63% Indigenous, 0.46% South Asian, 0.23% Black, 0.23% Hispanic, and 1.12% Other. Black individuals were of sub-Saharan Africa decent. The original PLCOm2012 model label *American Indian/Alaskan Native* was considered *Indigenous* and Australian natives and Channel Islanders/Torres Strait Islanders were in this category. The number of non-White individuals in the ILST was limited and in the current study stratification by race/ethnicity was not undertaken.

The PLCOm2012 and other similar models do not characterize the adjusted risk for Hispanics and Asians well. For this reason, the full PLCOm2012 was re-parameterized with Hispanics and Asians included with Whites, named the *PLCOm2012race3L*.[1] This version is more sensitive in predicting lung cancers in Hispanics and Asians and in external validation performed as well as the original model. Currently, many lung cancer screening programs, pilots and studies/trials are using the *PLCOm2012noRace* model, which has been re-parameterized to exclude the race/ethnicity predictor.

Several studies are planned in different Indigenous populations that will assess the PLCOm2012 including an Indigenous predictor and Indigenous eligibility will be compared with standard categorical age/pack-years/quit-year eligibility. Also, the magnitude of effect for the Indigenous predictor will be assessed. It may well be that the magnitude of effect for Indigenous may need to be adjusted in different populations, because the adjusted risk appears to vary in different Indigenous populations. For example, the adjusted lung cancer risk in Canadian Innuit appears to be greater than for many Canadian First Nations peoples, and in the New Zealand Māori risk may be underestimated by the PLCOm2012. (We have not specified the studies here as funding or Indigenous approval have not been finalized.)

In the PLCOm2012, *education* is coded in six ordinal levels. Although education in different jurisdiction varies, it was not difficult in the different ILST sites to classify education into six ordinal levels that roughly corresponded to education levels in the model. Education is an estimator of socioeconomic circumstance, and we believe that in the absence of education data, other ordinal estimators of socioeconomic circumstance in six levels could be effectively substituted for missing education.

In some circumstances people may wish to use the PLCOm2012 but do not have all 11 predictors available. Several versions of the PLCOm2012 are available in which selected predictors have been removed and the model has been re-parameterized. In most cases, the reduced model predicts almost as well as the full model. Such models are available from the corresponding author upon request.

Appendix Table 2. Accuracy parameters of the PLCOm2012 with ≥1.5%/6y threshold for positivity

Table 3a. Distribution of individuals stratified by lung cancer and PLCOm2012 ≥1.5% status in ILST

Criteria status	No lung cancer	Lung cancer	Totals
PLCOm2012 <1.5%	774	6	780
PLCOm2012 ≥1.5%	4868	171	5039
Totals	5642	177	5819

Table 3b. Distribution of individuals stratified by lung cancer and PLCOm2012 ≥1.5% status in ILST supplemented* by adding the number of individuals and lung cancers expected in individuals who are PLCOm2012 <1.5% and USPSTF2013-negative, who would not have qualified for the ILST

Criteria status	No lung cancer	Lung cancer	Totals
PLCOm2012 <1.5%	774 + 7093 = 7867	6 + 13 = 19	780 + 7106 = 7886
PLCOm2012 ≥1.5%	4868	171	5039
Totals	12735	190	12925

Table 3c. Accuracy parameters for the PLCOm2012 with ≥1.5%/6y threshold for positivity in ILST sample only and supplemented with data projected from PLCO statistics* (Data are from Tables S1a and S1b)

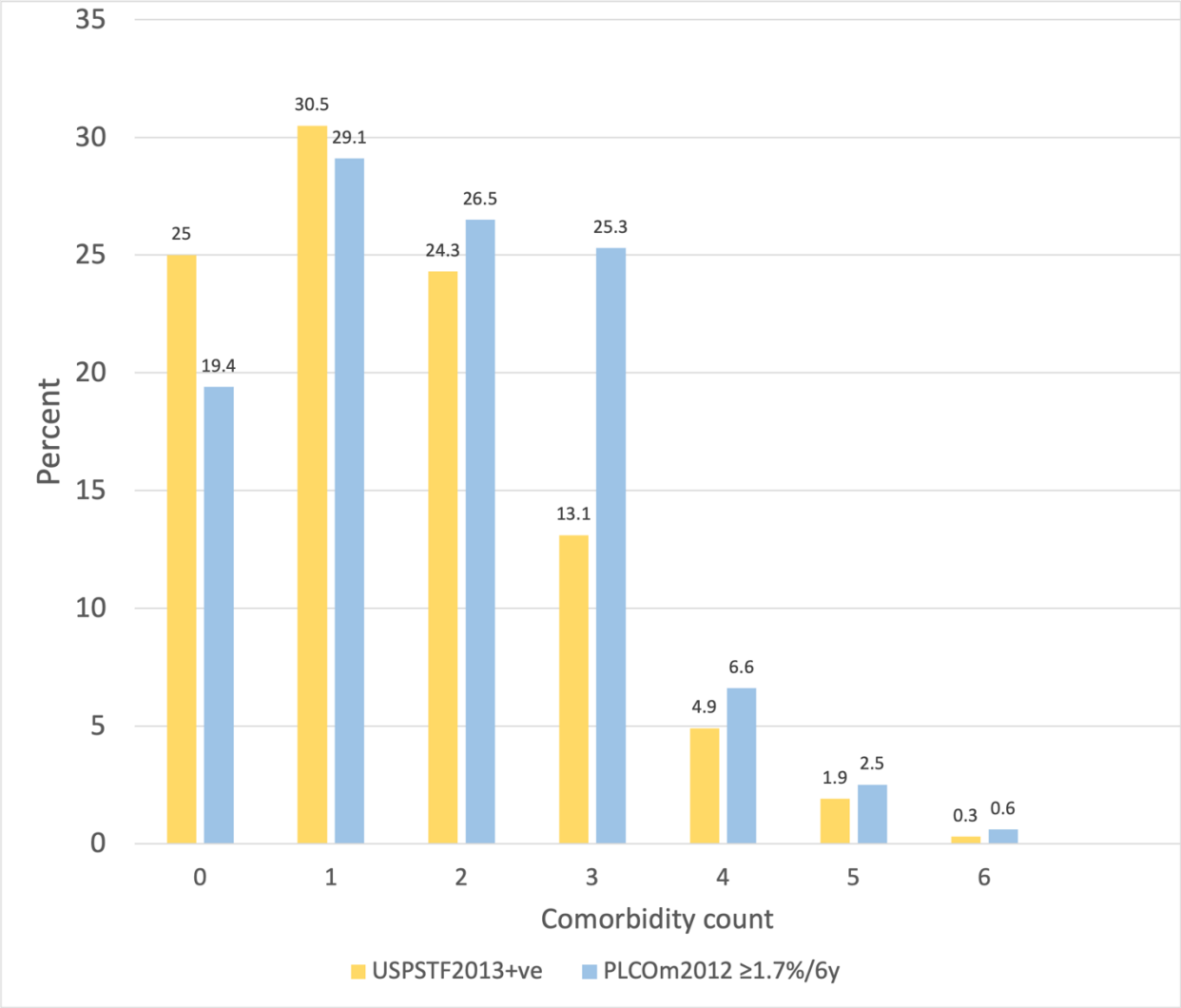
Sample	ILST only	ILST supplemented with data projected from PLCO statistics*
Sensitivity	96.6% (92.8-98.7%)	90.0% (84.8-93.9%)
Specificity	13.7% (12.8-14.6%)	61.8% (60.9-62.6%)
PPV	3.39% (2.91-3.93%)	3.39% (2.91-3.93%)
NPV	99.2% (98.3-99.7%)	99.8% (99.6-99.9%)

Abbreviations: ILST, International Lung Screening Trial; PLCO, Prostate Lung Colorectal and Ovarian Cancer Screening Trial; USPSTF United States Preventive Services Task Force.

* In the PLCO trial of 74,207 individuals who had smoked, there were 40,800 (54.98%) individuals who were USPSTF2013 negative and had PLCOm2012 risks <1.5%/6y. In this group, 189 lung cancers were observed in 6 years of follow-up (0.46%/6y). If this proportion and lung cancer rate are applied to the ILST sample, there would be 7106 individuals added to the USPSTF-negative/PLCOm2012<1.5%/6y group and 13 lung cancers would be expected in them in 2.3 years of follow-up.

Interpretation: These statistics provide approximate estimates of accuracy of the PLCOm2012≥1.5%/6y eligibility criteria, which is a threshold used in some studies, pilots and programs. Because this threshold found eligible a greater number of individuals than the USPSTF2013 criteria, direct comparisons cannot be made. The statistics presented in the last column of Table S1c best reflect those expected in the general population of those who ever smoked. The sensitivities reported here exclude all lung cancers in those individuals who never smoked and thus will over-estimate sensitivities in the overall general population ages 55 to 80 years by 15% or more.

Appendix Figure 1. Distribution of comorbidity count* by lung cancer screening eligibility criteria, USPSTF2013 positive and PLCOm2012 with ≥1.7%/6y



* The ten comorbidities that are summed to produce the comorbidity count (1 = present, 0 = absent) are heart disease, stroke, hypertension, chronic obstructive pulmonary disease, diabetes, cancer, gastrointestinal disease, liver disease, arthritis and osteoporosis/osteopenia.

Appendix Text 2. Weibull accelerated failure time parametric survival model predicting all-cause mortality

The following Weibull accelerated failure time parametric survival model was prepared using Prostate Lung Colorectal and Ovarian Cancer Screening Trial data and included only individuals who were USPSTF2013 criteria positive or who had PLCOm2012 risks ≥1.702%/6y.

The model predictor hazard ratios and beta coefficients and model parameters are presented in Table S3 below. The model is based on a Weibull time distribution. The accuracy of the Weibull model predicted survival times was tested by fitting the model estimated survival times to the actual observed survival times obtained from Kaplan-Meier estimates of survival. The visual correspondence is very good (Figure S3). The Weibull parametric model hazard ratios match very well with those obtained in a parallel Cox proportional hazards model, which does not make assumptions regarding time distributions.[2] A Cox model was not used in our analysis because it does not allow estimation of life expectancies in a straight-forward fashion, as the Weibull parametric model does.[3]

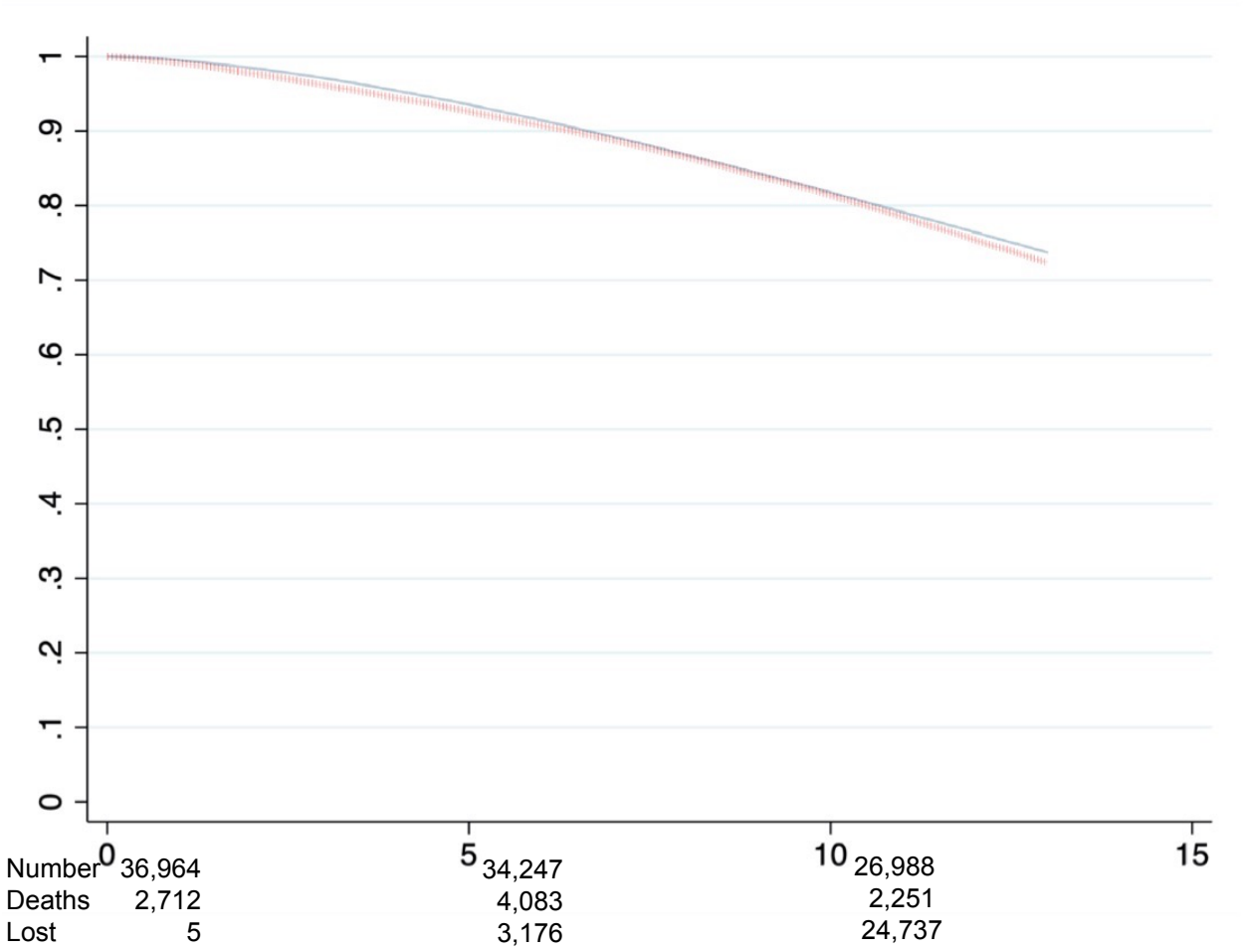
Appendix Table 3. Predictors and model parameters for the Weibull accelerated failure time parametric survival model predicting all-cause mortality in PLCO trial participants who were USPSTF2013 criteria positive or who had PLCOm2012 risks ≥1.702%/6y (N= 35,976)

Predictor	Hazard ratio	Confidence intervals, P-value	Beta coefficient*
Age (centered on 55 years)	1.09	1.08-1.09, p<0.001	-0.0520344
Sex (Male vs Female)	1.66	1.58-1.74, p<0.001	-0.3182803
Body mass index (kg/m^2)			
<18	1.76	1.60-1.95, p<0.001	-0.3579735
18 to <30	Referent	Referent	Referent
≥30	1.11	1.06-1.17 p<0.001	-0.0668251
Comorbidity count, per change of 1 level of 10†	1.29	1.27-1.32, p<0.001	-0.1628452
Lung cancer status			
Not diagnosed	Referent	Referent	Referent
Diagnosed, early stage	2.11	1.90-2.34, p<0.001	-0.4711164
Diagnosed, late stage	5.59	5.26-5.93, p<0.001	-1.084395
Smoking status			
Former	Referent	Referent	Referent
Current	1.28	1.21-1.35, p<0.001	-0.1549721
Smoking intensity, cig/day	1.005	1.004-1.006, p<0.001	-0.0031301
Smoking duration, years	1.007	1.003-1.012, p<0.001	-0.0046028
Smoking quit years in those who used to smoke	0.989	0.983-0.995, p<0.001	0.0069549
Model Parameter			
Constant			4.779189
p (the shape parameter)			1.586393
ln p			.4614628
1/p			.6303609

* Note that the beta coefficients are expressed as negative terms, because in the accelerated failure time version of the Weibull model, the coefficient estimates a factor by which life expectancy is reduced.

† The ten comorbidities that are summed to produce the comorbidity count (1 = present, 0 = absent) are heart disease, stroke, hypertension, chronic obstructive pulmonary disease, diabetes, cancer, gastrointestinal disease, liver disease, arthritis and osteoporosis/osteopenia.

Appendix Figure 2. Weibull survival model for all-causes death (solid blue line) superimposed on Kaplan-Meier survival plot of observed outcomes (hashed red line). Prostate Lung Colorectal and Ovarian Cancer Screening Trial data. Only individuals who were USPSTF2013 criteria positive or who had PLCOm2012 risks ≥1.702%/6y are included.



Appendix References

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2. Cleves MA, Gould W, Marchenko YV. An introduction to survival analysis using Stata. Revised third edition. ed. College Station, Texas: Stata Press; 2016.
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