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Appendix E1

Section 1: Input Parameters

Nodule Size and Growth

Each simulated patient in the model is initially assigned a baseline nodule size drawn from a distribution of ground glass nodule (GGN) diameters from National Lung Cancer Screening Trial (NLST) data. This distribution includes sizes from 906 patients, with sizes having range 2.5–59.5 mm, average 8.4 mm, and standard deviation 5.5 mm. For NLST participants with more than one GGN, the diameter of the largest nodule was used. For each nodule, the diameter is calculated by averaging the longest overall and longest perpendicular diameter.

To capture correlation of higher growth rate with larger initial (baseline) nodule size, we used the following procedure to assign growth rates. First, a distribution of ground glass nodule growth rates was estimated from Figure 2a in Kakinuma et al (8), which shows the cumulative proportion of nodules that have grown over time; the growth rate distribution is shown in Figure E1. For this estimation, we model nodule growth rate as linear (Lee et al, 10). Then, we used the conditional probability of growth rate conditional on the initial nodule size stratum of either > 10 mm or ≤ 10 mm given in Table 2 of Kakinuma et al. The following can be inferred from these conditional probabilities: of GGNs > 10 mm in initial size, 13% will grow ≥ 1 mm/year, 41% will grow 0.4 to 1 mm/year, and 46% will grow 0 to 0.4 mm/year. For GGNs ≤ 10 mm in initial size, 1% will grow ≥ 1 mm/year, 10% will grow 0.4 to 1 mm/year, and 89% will grow 0 to 0.4 mm/year. (These percentages were derived using the facts that ≥2 mm/2 yr is equivalent to ≥1 mm/yr, and ≥2 mm/5 yr is equivalent to ≥0.4 mm/yr.) To derive representative sizes of nodules above and below 10 mm in our simulated cohort, we calculated the average initial nodule sizes in these two strata using data from NLST (17.11 and 4.75 mm, respectively). We used these two size strata to linearly interpolate the conditional growth rate probabilities given a particular nodule size with the constraint that the sum of all nodule sizes will regenerate the distribution of GGN growth rates in Figure E1. An example of the growth rate distribution for a nodule with initial size 25 mm is shown in Figure E2.

Table E1 shows the average growth rate among the model's simulated ground glass nodules of a given initial size range, and Figure E3 shows the cumulative percentage of simulated nodules in which measurable growth has been observed over time, with stratification by initial nodule size. Simulated nodules with larger initial size are more likely to show growth over time and to have higher growth rates if they do grow.

Each GGN in the model was assigned a probability of developing a solid component over the course of ten years of follow-up, and for those GGNs that would become part-solid, a length of time until solid component development was assigned. These parameters were based on transformed distributions derived from Kakinuma et al (8), similar to the growth rate parameter described above. A larger initial size is associated with a higher likelihood of developing a solid component and a shorter length of time before it appears in follow-up. Figure E4 shows a

cumulative solid component development curve for simulated nodules in the model. All solid components were assigned an initial solid component size of 1.5 mm at time of discovery on CT.

For those GGNs that develop solid components, growth rates were assigned to the solid components with a method analogous to the assignment of overall nodule growth rates described above. Larger initial nodule size was associated with a higher growth rate for any solid component that might develop.

Based on data observed in the International Early Lung and Cardiac Action Program (I-ELCAP) lung screening study (2), each GGN was assigned a probability of resolving after the baseline screen but prior to the first follow-up computed tomography (CT) scan. An initial size distribution specific to these resolving nodules was also used from I-ELCAP (2) to assign a baseline size to the resolving nodules.

Nodule Malignancy

A nodule was identified as having a clinically significant malignancy if one of its growth rates (either of the nodule or of the solid component) exceeded thresholds for malignant growth. The two thresholds were determined through a model calibration process, in which the calibration targets were incidences of malignancy conditional on nodule consistency and size.

The targets were derived using the NLST Nodule Searcher calculator for solitary pulmonary nodule risk (available at http://pulmnodules.com and described in Morrison et al (18)), in conjunction with expert opinion (M.M.H. and E.J.B. Jr.). To calibrate the model, the simulation was run 10,000 times, with each run using a number randomly drawn from the range of possible growth rates as the candidate malignancy threshold. Each of the 10,000 runs was then ranked in order of fit, using the sum of squared residuals, to the calibration targets. Following the previously established calibration methodology (Hur et al and Yeh et al 33,36). the malignancy thresholds of the top 1% best-fitting model runs were averaged to obtain the thresholds used in the production version of the model. These thresholds are approximately 2.6 mm/year for nodule growth and 0.9 mm/year for solid component growth. Table 2 in the main text shows the prevalence of clinically significant malignancy in persistent nodules by Lung-RADS Category in our simulation with the use of these thresholds.

Patient Characteristics

The age of a simulated patient was sampled from the age distribution of NLST participants whose information had previously been used for creating the initial nodule size distribution. Age at beginning of follow-up was calculated as age at time of randomization for NLST plus the number of years until the participant's final screening.

Patients undergoing follow-up were assumed to be either current or former smokers at the time of baseline screen, with a 48% chance of being assigned a status of current smoker, based on NLST data. Never-smoking patients were not included in the model to make the follow-up cohort representative of the patients undergoing lung cancer screening according to the recommendations of the U. S. Preventative Services Task Force, which do not apply to never-smokers. Monthly background death probability for cancer-free current and former smokers undergoing follow-up was calculated using input data from the Smoking History Generator (23,24) to account for differences in smoking behavior between different birth cohorts. Birth year and age at a given month during follow-up (calculated based on patient's initial age and the

assumption that follow-up began in the year 2017) were taken into consideration in assigning death probabilities.

Section 2: Model Structure and Implementation of Lung-RADS Follow-up Procedures

The follow-up procedure simulated in the model was based on the specifications in the Lung Imaging Reporting and Data System ("Lung-RADS") created by the American College of Radiology. The Lung-RADS category of each nodule in the model was evaluated each month in which the patient received a CT scan, based on the current size, consistency, and observed growth of the nodule. We defined measurable growth in nodule size or solid component size–ie, the amount of observed growth required to consider the nodule "growing" in our model–to be 1.5 mm of growth in the diameter observed since a prior follow-up. This is in line with Lung-RADS, which defines observed "growth" as "an increase in size of >1.5 mm" (16).

Lung-RADS 4B nodules, as defined by part-solid nodules with solid component ≥ 8 mm or a new solid component ≥ 4 mm, were sent to treatment. Some Category 3, 4A, or 4B nodules in the model were elevated to Category 4X due to "suspicious" features (M.M.H. and E.J.B.Jr.). In particular, for patients with part-solid nodules in which the solid component eclipses the nodule in size (ie, fully solid nodules), the patient is deemed Category 4X if the solid component is over 6 mm in size. Large (≥ 20 mm) GGNs that showed growth of at least 3 mm in overall size since baseline were deemed Category 4X and treated. A tabular depiction of our follow-up procedure is given in Table E2.

A schematic diagram illustrating the model's structure is shown in Figure 1 in the main text. All simulated patients begin with a baseline CT scan in which a GGN is discovered. Based on the results of this screen, the patient will be assigned to wait either 12 or 6 months (ie, will be assigned a Lung-RADS category of 2 or 3) before the next follow-up per Lung-RADS. After this, the patient receives their first follow-up CT. Based on observation of the nodule at this time, the patient is either removed from follow-up due to their nodule having resolved, or continues follow-up. If the patient continues, each subsequent CT scan will either be followed by a waiting period of 12, 6, or 3 months before the next follow-up scan (ie, will assign Lung-RADS category 2, 3, or 4A), or will result in the patient being sent to treatment (ie, will assign Lung-RADS category 4B or 4X).

Once sent to treatment, monthly mortality rates will vary based on patient factors (as described elsewhere in the Supplement), including treatment modality and the probability of complications at the time of treatment. At each month, the patient has a probability, dependent on patient factors, of passing from their current state to a "death" state; we do not explicitly illustrate this in the diagram.

The occurrence and treatment of incident lung cancer during follow-up was modeled for using a separate simulation model. We used the Lung Cancer Policy Model (LCPM) (31,37) to calculate population-level incidental cancer mortality rates for the subsolid nodule follow-up cohort, assuming either annual, biennial, or triennial CT examinations. Table E3 shows the 10-year incident-cancer attributable death rate from the LCPM analysis, as well as the rates per screen of screen-detected incidental cancer, and the rates per screen for interval (non-screen-detected) incident cancer.

Section 3: Treatment Parameters

Treatment Options

In the base case analysis, patients with a Lung-RADS category 4B/4X nodule were treated with either surgery or stereotactic body radiation therapy (SBRT). Surgery was assigned if the patient sent to treatment was no older than 77, and otherwise SBRT was assigned. An additional analysis also included a "no treatment" scenario, in which a patient who would have received treatment in the base case analysis is instead assigned to wait three months and then re-enter the follow-up process.

Treatment and Cancer Mortality

Table E4 shows values for parameters related to treatment and cancer mortality. Survival after treatment is dependent on whether the patient has a clinically significant malignancy at time of treatment. If not, then posttreatment survival is the same as that described in Section 1, and a patient's probability of surgery complication death in the month of surgery is based on age-adjusted 30-day surgical complication mortality rate (21), or in the case of SBRT is based on a SBRT complication mortality rate (30).

Survival of patients with clinically significant part-solid cancer treated with surgery is based on a database analysis of lung cancer patients by stage (25). A malignant nodule in the model may represent stage 1A, 1B, 2A, 2B, or (rarely) 3 lung cancer, with stage dictated by nodule size according to the cutoffs specified in the TNM lung cancer staging classification system (25). Survival is adjusted for age (20), current smoker status (22) and part-solid nodule consistency (14). For patients treated with SBRT, the death probability is further adjusted with a hazard ratio relating postsurgery and post-SBRT survival (26). See Table E5 for examples of probabilities assigned to patients with malignancies.

Our model assumes that these probabilities apply only to treated cancer patients with part-solid nodules, whereas those with GGNs have a death probability derived from (14).

The background death probabilities for untreated patients described in Section 1 apply only to patients in the simulation who do not have a clinically significant malignancy. For the cases of untreated patients with clinically significant malignancy, probability of dying at a given month is based on results from a meta-analysis (27) of survival data for patients with untreated non-small cell lung cancer. The death probability is adjusted based on age and part-solid nodule consistency. The malignancy of untreated patients was classified as early-stage or late-stage depending on the size of the malignant nodule. The malignancy was identified as late-stage only if the nodule diameter was at least 70 mm, which is the size threshold for "T3" cancer according to the TNM lung cancer staging system.

Section 4: Sensitivity Analysis

We performed one-way sensitivity analyses to quantify the effect of parameter uncertainty on our primary outcomes of interest: 10-year overall survival of patients with nonresolving nonsolid nodules, given 1-, 2-, or 3-year follow-up interval lengths; and 10-year overall survival for different treatment modalities (surgery, SBRT, or no treatment) given the default 1-year follow-up interval length. Tables E6A and E6B show the results of these sensitivity analyses.

Malignancy Thresholds

We investigated how variations in malignancy prevalence would affect our results. In the base case analysis, nodule and solid component growth rate thresholds for clinically significant malignancy were determined through calibration of the model to prevalence of malignant nodules in the NLST. As stated in Section 1, each of the two thresholds was computed by averaging the candidate threshold values that were in the top 1% (of 10,000) model calibration runs ranked according to fit to calibration targets. For sensitivity analysis, following a previously established method (33,36), upper and lower bound values on the threshold values were selected using the set of top 1% of best-fitting model calibration runs. The lowest growth rates of these top 1% of runs were used as the lower bounds for sensitivity analysis, and the highest of the top 1% were used as the upper bounds.

Other Parameters

We varied several mortality parameters within a percentage of their assigned values in the base-case model. The part-solid lung cancer mortality scale factor is an estimate of how much less likely patients with nonsolid nodule cancer are to die compared with patients with solid cancer. We set this parameter to ± 10% of its base-case value. We also reduced untreated cancer mortality rates by 10% and by 50% to account for selection bias in the study of untreated cancer patients that informed these rates in our model. Since surgical mortality rates can vary by surgeon and by hospital (38), we also set surgical complications mortality to ± 10% of its base-case value.

References

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Table E1: Average Growth Rates of Ground Glass Nodules within a Given Range of Size at Baseline

Initial size range (mm)	Average growth rate (mm/year)
0–10	0.1
10–20	0.3
20–30	0.6
30+	0.9

Table E2: Implementation of Lung-RADS Follow-up Procedure

Lung-RADS Category	Definition	Management
2	GGN < 20 mm or GGN ≥ 20 mm with growth < 3 mm	1-year follow-up
	Category 3 or 4 nodule stable	
3	PSN ≥ 6 mm with solid component < 6 mm	6-month follow-up
	GGN ≥ 20 mm at baseline	
4A	PSN ≥ 6 mm with solid component ≥ 6 mm and < 8 mm	3-month follow-up
	PSN ≥ 6 mm with growing < 4 mm solid component	
4B	PSN with solid component ≥ 8 mm	Treatment
	PSN with growing ≥ 4 mm solid component	
4×	GGN ≥ 20 mm with growth > 3 mm*	Treatment
	PSN that becomes fully solid if size ≥ 6 mm*	

Growth defined as an increase in 1.5 mm over baseline.

* Rules for categorizing a nodule as 4X (“suspicious features”) are not given explicitly by Lung-RADS. These rules were derived from expert opinion.

Table E3: Incidental Lung Cancer Rates and Mortality over 10 Years of Nonsolid Nodule Follow-up, with Varying Follow-up Interval Lengths

Incident cancer parameters	Intervals between CT exams		
	1 year	2 years	3 years
10-year death rates (%)	4.83	4.87	4.89
Screen-detected lung cancer rate (% of population per screen)	0.13	0.11	0.09
Interval lung cancer rate (% of population between screens)	0.22	0.23	0.23

Table E4: Values of Treatment and Survival Parameters

Parameter Description	Parameter Value(s)	Source
Age-adjusted 30-day surgical complication mortality rate (%)	Age 55–59: 1.9	12
	Age 60–64: 1.7	
	Age 65–69: 2.6	
	Age 70–74: 3.8	
	Age 75–79: 4.8	
	Age 80–84: 4.7	
	Age 85+: 9.0	
SBRT complication mortality rate	0.004	13
Hazard ratio relating SBRT mortality to surgery mortality	1.4	18
Scale factor relating part-solid nodule lung cancer mortality to solid nodule lung cancer mortality	2.5/12.4	17
Hazard ratios for lung cancer patient mortality by age group	Age 55–64: 1.0	15
	Age 65–74: 1.6	
	Age 75–85: 2.4	
Hazard ratio relating lung cancer patient mortality for current smokers to mortality for former smokers	1.3	16

Monthly death probability for untreated patients with lung cancer (%) *(unadjusted)*	Early stage: 3.6	19
	Late stage: 8.6	
Monthly death probability for treated patients with lung cancer by stage (%) *(unadjusted)*	Stage 1A: 0.3	14
	Stage 1B: 0.6	
	Stage 2A: 0.9	
	Stage 2B: 1.2	
	Stage 3: 2.0	

SBRT: stereotactic body radiation therapy.

Table E5: Selected Yearly Death Probabilities for a Current Smoker with a Clinically Significant Part-Solid Malignancy Who Began Screening at Age 55

Current Age	Part-solid Cancer Treated with Surgery: stage 1A	Part-solid Cancer Treated with Surgery: stage 2A	Untreated Part-solid Cancer: stage 1A/B or 2A/B
60	2.4%	4.3%	8.3%
65	3.6%	6.5%	13%

Table E6A: Sensitivity Analysis: Effects on 10-Year Overall Survival for Patients with Persistent Subsolid Nodules Given 1-, 2-, or 3-Year Follow-up Interval Lengths for Category 2 Nodules

Model conditions	Parameter details	10-year OS (%)		
		1-yr FIL	2-yr FIL	3-yr FIL
Base-case conditions	Overall size growth threshold: 0.217 mm/month	71.59 (527827/737306)	71.50 (527147/737306)	71.41 (526507/737306)
	Solid component size growth threshold: 0.078 mm/month			
	Part-solid lung cancer mortality scale factor: 0.202			
	Monthly death probability for early stage untreated cancer (unadjusted): 3.6%			
	Monthly death probability for late stage untreated cancer (unadjusted): 8.6%			
	Age-based surgical complications mortality rate: Ranging from 1.7%–9.0%			
Lower bounds for malignancy thresholds	Overall size growth threshold: 0.180 mm/month	71.35 (526068/737306)	71.26 (525404/737306)	71.17 (524741/737306)
	Solid component size growth threshold: 0.049 mm/month			
Upper bounds for malignancy thresholds	Overall size growth threshold: 0.250 mm/month	71.72 (528796/737306)	71.64 (528206/737306)	71.57 (527690/737306)
	Solid component size growth threshold: 0.115 mm/month			
Part-solid lung cancer mortality scale factor decreased by 10%	Part-solid lung cancer mortality scale factor: 0.181	71.62 (528059/737306)	71.53 (527395/737306)	71.45 (526805/737306)
Part-solid lung cancer mortality scale factor increased by 10%	Part-solid lung cancer mortality scale factor: 0.222	71.56 (527616/737306)	71.47 (526953/737306)	71.37 (526215/737306)
Untreated cancer long-term mortality decreased by 10%	Monthly death probability for early stage untreated SSN cancer (unadjusted): 2.1%	71.69 (528575/737306)	71.61 (527985/737306)	71.55 (527542/737306)
	Monthly death probability for late stage untreated SSN cancer (unadjusted): 5.4%			
Surgical complications mortality decreased by 10%	Age-based surgical complications mortality rate: Ranging from 1.5%–8.1%	71.61 (527985/737306)	71.52 (527321/737306)	71.43 (526658/737306)
Untreated cancer long-term mortality decreased by 50%	Monthly death probability for early stage untreated SSN cancer (unadjusted): 0.7%	71.80 (529386/737306)	71.76 (529091/737306)	71.73 (528870/737306)
	Monthly death probability for late stage untreated SSN cancer (unadjusted): 1.8%			

Surgical complications mortality increased by 10%	Age-based surgical complications mortality rate: Ranging from 1.9%–9.9%	71.58 (527764/737306)	71.50 (527174/737306)	71.39 (526363/737306)

OS = overall survival, FIL = Follow-up interval length.

Table E6B: Sensitivity Analysis: Effects on 10-Year Overall Survival for Patients with Category 4B/4X Subsolid Nodules Given Surgery, SBRT, or No Therapy as Treatment

Model conditions	Parameter details	10-year OS (%)		
		Surgery	SBRT	No therapy
Base-case conditions	Overall size growth threshold: 0.217 mm/month	78.55 (49139/62559)	79.84 (49945/62559)	74.35 (46512/62559)
	Solid component size growth threshold: 0.078 mm/month			
	Part-solid lung cancer mortality scale factor: 0.202			
	Monthly death probability for early stage untreated cancer (unadjusted): 3.6%			
	Monthly death probability for late stage untreated cancer (unadjusted): 8.6%			
	Age-based surgical complications mortality rate: Ranging from 1.7%–9.0%			
Lower bounds for malignancy thresholds	Overall size growth threshold: 0.180 mm/month	78.17 (48902/62559)	79.24 (49572/62559)	72.69 (45474/62559)
	Solid component size growth threshold: 0.049 mm/month			
Upper bounds for malignancy thresholds	Overall size growth threshold: 0.250 mm/month	78.90 (49359/62559)	80.40 (50297/62559)	76.35 (47764/62559)
	Solid component size growth threshold: 0.115 mm/month			
Part-solid lung cancer mortality scale factor decreased by 10%	Part-solid lung cancer mortality scale factor: 0.181	78.67 (49215/62559)	79.94 (50010/62559)	74.66 (46707/62559)
Part-solid lung cancer mortality scale factor increased by 10%	Part-solid lung cancer mortality scale factor: 0.222	78.45 (49078/62559)	79.72 (49872/62559)	74.06 (46331/62559)
Untreated cancer long-term mortality decreased by 10%	Monthly death probability for early stage untreated SSN cancer (unadjusted): 2.1%	78.57 (49153/62559)	79.80 (49922/62559)	76.51 (47864/62559)
	Monthly death probability for late stage untreated SSN cancer (unadjusted): 5.4%			
Untreated cancer long-term mortality decreased by 50%	Monthly death probability for early stage untreated SSN cancer (unadjusted): 0.7%	78.59 (49165/62559)	79.77 (49903/62559)	80.81 (50554/62559)
	Monthly death probability for late stage untreated SSN cancer (unadjusted): 1.8%			
Surgical complications mortality decreased by 10%	Age-based surgical complications mortality rate: Ranging from 1.5%–8.1%	78.77 (49278/62559)	79.84 (49947/62559)	74.35 (46513/62559)
Surgical complications mortality increased by 10%	Age-based surgical complications mortality rate: Ranging from 1.9%–9.9%	78.29 (48977/62559)	79.84 (49947/62559)	74.35 (46513/62559)

OS = overall survival, SBRT = Stereotactic body radiation therapy.