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Evaluating the Patient With a Pulmonary Nodule
A Review

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IMPORTANCE Pulmonary nodules are identified in approximately 1.6 million patients per year in the US and are detected on approximately 30% of computed tomographic (CT) images of the chest. Optimal treatment of an individual with a pulmonary nodule can lead to early detection of cancer while minimizing testing for a benign nodule.

OBSERVATIONS At least 95% of all pulmonary nodules identified are benign, most often granulomas or intrapulmonary lymph nodes. Smaller nodules are more likely to be benign. Pulmonary nodules are categorized as small solid (<8 mm), larger solid (≥8 mm), and subsolid. Subsolid nodules are divided into ground-glass nodules (no solid component) and part-solid (both ground-glass and solid components). The probability of malignancy is less than 1% for all nodules smaller than 6 mm and 1% to 2% for nodules 6 mm to 8 mm. Nodules that are 6 mm to 8 mm can be followed with a repeat chest CT in 6 to 12 months, depending on the presence of patient risk factors and imaging characteristics associated with lung malignancy, clinical judgment about the probability of malignancy, and patient preferences. The treatment of an individual with a solid pulmonary nodule 8 mm or larger is based on the estimated probability of malignancy; the presence of patient comorbidities, such as chronic obstructive pulmonary disease and coronary artery disease; and patient preferences. Management options include surveillance imaging, defined as monitoring for nodule growth with chest CT imaging, positron emission tomography–CT imaging, nonsurgical biopsy with bronchoscopy or transthoracic needle biopsy, and surgical resection. Part-solid pulmonary nodules are managed according to the size of the solid component. Larger solid components are associated with a higher risk of malignancy. Ground-glass pulmonary nodules have a probability of malignancy of 10% to 50% when they persist beyond 3 months and are larger than 10 mm in diameter. A malignant nodule that is entirely ground glass in appearance is typically slow growing. Current bronchoscopy and transthoracic needle biopsy methods yield a sensitivity of 70% to 90% for a diagnosis of lung cancer.

CONCLUSIONS AND RELEVANCE Pulmonary nodules are identified in approximately 1.6 million people per year in the US and approximately 30% of chest CT images. The treatment of an individual with a pulmonary nodule should be guided by the probability that the nodule is malignant, safety of testing, the likelihood that additional testing will be informative, and patient preferences.

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A pulmonary nodule is a small (<3 cm), focal, distinct radiographic density completely surrounded by lung tissue. Pulmonary nodules are identified in approximately 1.6 million people per year in the US and are detected on approximately 30% of computed tomographic (CT) images of the chest.[1] More than 50% of patients with a pulmonary nodule have more than 1 nodule.[2] Ideal evaluation of an individual with a pulmonary nodule would expedite therapy for a malignant nodule and minimize testing for those with a benign nodule.

This review focuses on evaluation of individuals with a single dominant pulmonary nodule. The term *dominant* refers to the largest or the most suspicious-appearing nodule. This review does not discuss management of pulmonary nodules in patients with known malignancy, patients with multiple pulmonary nodules without a dominant pulmonary nodule, or patients with a pulmonary mass, defined as a lung opacity with a diameter greater than 3 cm. The management approach to these individuals differs from that of an individual with a dominant pulmonary nodule, and pulmonary masses have a high probability of malignancy. This review describes current evidence regarding the optimal methods to establish the diagnosis of a dominant pulmonary nodule that may be due to primary lung malignancy, metastatic disease, a noninfectious inflammatory process, infection, or scar residual from a prior infection.

This review describes the epidemiology of pulmonary nodules and current evidence-based approaches to treatment of an

individual with a pulmonary nodule that is identified incidentally on chest x-ray, chest CT, or during low-dose CT screening (LDCT) for lung cancer.

Methods

PubMed and Cochrane databases were searched for English-language articles related to the epidemiology and treatment of adults with pulmonary nodules that were published from January 1, 2011, through September 28, 2021. Search terms included *lung nodule(s)*, *pulmonary nodule(s)*, and any combination, modified by *solitary*, *multiple*, *screening*, *screen-detected*, and *incidental*. Results were further categorized by the following terms: *guidelines*, *risk*, *risk assessment*, *calculator*, *model*, *algorithm*, *diagnosis*, *diagnostic techniques*, *procedures*, *biopsy*, *bronchoscopy*, *surgery*, *resection*, *(disease) management*, *treatment*, *therapy*, *tumor board*, and *clinic*. A total of 286 articles were retrieved. Results were supplemented with relevant articles from the references of selected articles and the authors' files. A total of 51 articles were selected for inclusion, including 9 clinical practice guidelines, 11 clinical trials (6 randomized, 5 nonrandomized), 5 prospective cohort studies, 14 retrospective cohort studies, 5 risk calculator development or validation studies, 3 systematic reviews with meta-analyses, 3 biomarker accuracy studies, and 1 questionnaire study. Articles were selected with the intent of identifying those with the highest-quality study design for each section of the review and relevance to a general medical readership.

Discussion

Epidemiology

Approximately 95% of all pulmonary nodules identified on CT scans are benign.[1] The prevalence of pulmonary nodules in high-risk populations, such as those who are eligible for LDCT screening (ie, those aged 50-80 years with ≥20 pack-years' smoking history who have smoked within the past 15 years),[3] those with a cancer history, family history of lung cancer, or another significant risk factor (ie, asbestos exposure), has varied, in part based on the size threshold used to define a nodule. In a Veterans Health Administration lung cancer screening implementation study that included any size pulmonary nodule in the definition of a positive finding, 1257 of 2106 screened individuals (59.7%) had a pulmonary nodule.[4] In the National Lung Screening Trial, nodules 4 mm or larger were identified in 27.3% (7191 of 26 309) of baseline LDCT scans.[5] Among 24 604 patients undergoing a second LDCT screening test (12 months after the baseline CT), 644 (2.6%) were identified as having a new nodule since the prior screening CT scan.[6] In the NELSON trial of 6309 patients undergoing screening for lung cancer, 147 patients (2.3%) had a nodule identified during baseline screening that grew at a concerning pace measured 3 months later, defined as a volume doubling time of less than 400 days.[7] In 2 studies of screening chest x-rays involving 103 500 participants, a pulmonary nodule was identified in 7.8% to 8.9% of the chest x-rays.[8,9] Imaging of the neck, abdomen, and heart can also identify pulmonary nodules. Of 1000 CT angiograms performed as a diagnostic test for pulmonary embo-

lism in an emergency department, 99 (9.9%) had nodules that required follow-up.[10]

The incidence of a pulmonary nodule increases with age, from 0.4 per 1000 person-years in people aged 18 to 24 years to 20.3 per 1000 person-years in those aged 85 to 89 years. In part, this increase is explained by the increase in chest CT imaging that occurs with age. The incidence of a pulmonary nodule is slightly higher in women (5.8 per 1000 person-years) than in men (5.2 per 1000 person-years) overall; however, for those older than 70 years, the incidence is higher in men.[1] In lung cancer screening trials, the rate of identifying a pulmonary nodule on baseline LDCT was similar in men (27.0%) and women (27.8%).[9] In chest x-rays, the rate of identifying a pulmonary nodule was slightly higher in men than women (9.6%-9.8% vs 8.2%-8.3%).[8,9] Rates of nodule identification on LDCT also increase with age. For example, in a study of 26 309 people aged 55 to 74 years who received an LDCT, the prevalence of pulmonary nodules was 24.3% in those aged 55 to 59 years and 34.0% in those aged 70 to 74 years.[9] In this study, the prevalence of pulmonary nodules was 23.2% in individuals with 30 to 35 pack-year smoking histories and 30.3% in those with more than 50 pack-years' smoking histories.[8,9] Although the rate of identification of pulmonary nodules on chest x-ray is much lower than on chest CT scan, similar trends in the prevalence of pulmonary nodules were observed in those screened with chest x-ray (8.0% in those who never smoked, 9.5% in those who previously smoked, 11.0% in those who currently smoke).[8,9]

The frequency of identifying pulmonary nodules is particularly high in individuals undergoing imaging for evaluation of a known extrapulmonary malignancy, reaching 75% (233 of 308) of patients in 1 study.[11] Other factors associated with a higher risk of a pulmonary nodule in a cohort of 26 004 individuals undergoing a baseline LDCT included a history of hard-rock mining (35.0% vs 27.3%; odds ratio [OR], 1.40 [95% CI, 1.04-1.89]), White race (28.0% vs 20.6%; OR, 1.39 [95% CI, 1.25-1.55]), residence in an area endemic for *Histoplasma* such as the Ohio River Valley (OR, 1.30 [95% CI, 1.21-1.40]; calculated absolute rates: 32.5% vs 26.4%), farm work (OR, 1.13 [95% CI, 1.03-1.23]; calculated absolute rates: 30.2% vs 27.1%), and a history of chronic obstructive pulmonary disease (OR, 1.08 [95% CI, 1.01-1.17], calculated absolute rates: 30.1% vs 26.8%).[12]

Pulmonary Nodule Evaluation

A focused history may identify recent exposure to an endemic infection such as histoplasmosis or coccidioidomycosis, symptoms related to infection, systemic inflammatory disease or malignancy, and personal histories of malignancy or comorbid conditions that can manifest as a pulmonary nodule.

When evaluating a newly diagnosed pulmonary nodule, it is important to review prior imaging, if available, to determine whether the size and other characteristics of the pulmonary nodule have changed. This may include abdominal imaging if the nodule is at the base of the lungs, head and neck imaging if the nodule is in the upper lung zones, or cardiac imaging. It is not necessary to perform a diagnostic CT of the entire chest if a low-risk pulmonary nodule is first noted on a different type of CT scan. Moreover, a solid nodule that has remained unchanged in size on a chest CT over a period of 2 years or longer is considered benign.

Figure. Pulmonary Nodule Examples on Computed Tomography
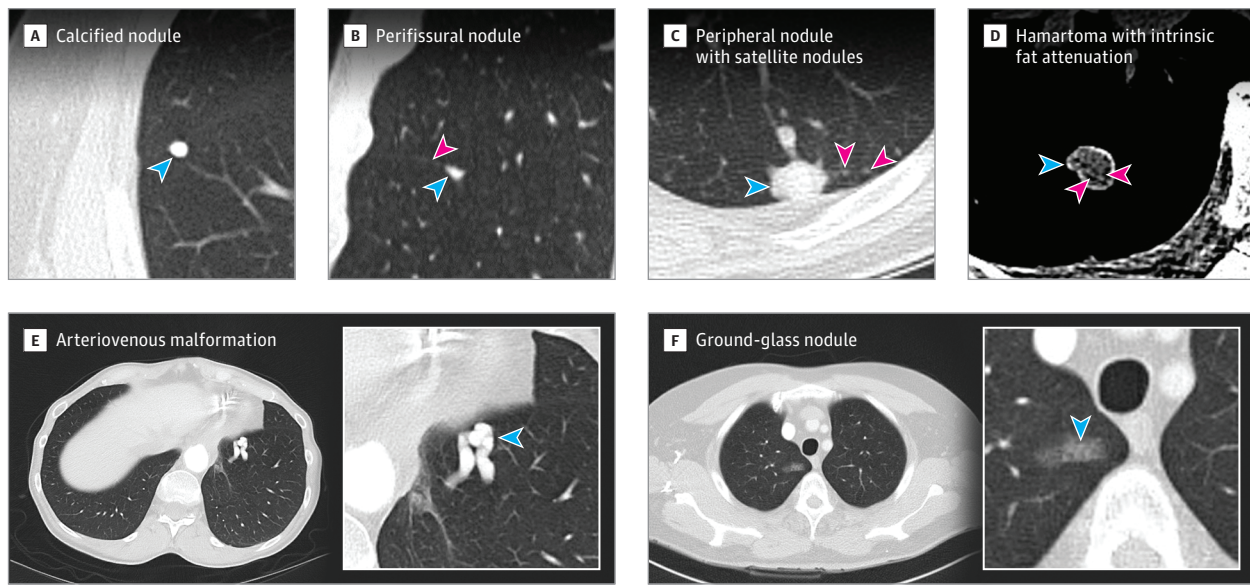
Panel A shows a calcified pulmonary nodule (blue arrowhead) consistent with benign calcified granulomas. Panel B shows a typical perifissural nodule (blue arrowhead) abutting the fissure (pink arrowhead). Panel C shows a peripheral pulmonary nodule (blue arrowhead) with adjacent satellite nodules (pink arrowheads) consistent with granulomatous process.

Panel D shows a pulmonary hamartoma (blue arrowhead) with areas of intrinsic fat attenuation that appear as black spots on a soft tissue window (pink arrowheads). Panel E shows a feeding and draining vessel of an arteriovenous malformation (blue arrowhead). Panel F shows a ground-glass nodule without a definable solid component (blue arrowhead).

Box 1. Commonly Asked Questions

Are there any situations in which a pulmonary nodule does not require subsequent imaging or further evaluation?
If a pulmonary nodule has a very low probability of being malignant, further follow-up with imaging is not warranted. Examples include patients with prior imaging showing that the nodule has been stable for 2 years or longer; a nodule that has imaging features confirming a benign diagnosis (eg, dense central calcification, fat density within the nodule); or a solid or a pure ground-glass nodule <6 mm in diameter in an individual without any lung cancer risk factors.

Are there scenarios where practice guidelines do not apply?
Practice guidelines may not apply to patients for whom the risk of malignancy differs from the general population. For example, patients with a known malignancy or recent history of malignancy; patients with organ transplant or other immunocompromised state; or patients aged <35 years. For these individuals, referral to a pulmonologist or to a multidisciplinary pulmonary nodule specialty clinic may be warranted.

When should a primary care physician consider referring a patient with a pulmonary nodule to a specialist?
Primary care physicians should refer a patient for specialty evaluation when they are uncomfortable with or uncertain about the most optimal evaluation plan. In addition, primary care physicians should consider referring patients with a large solid pulmonary nodule (≥8-30 mm) or a subsolid pulmonary nodule due to their higher risk of malignancy.

Imaging features should be carefully reviewed. CT images should be reconstructed in axial, coronal, and sagittal planes to provide the most detailed characterization of nodule features.

A benign pattern of calcification (eg, dense central [ie, a nodule with a large calcification in the middle vs a small one at the edge], laminated, stippled, or popcorn patterns of calcification; **Figure**, A) can obviate the need for follow-up imaging. In addition, a perifissural nodule, consisting of a smooth, well-circumscribed nodule adjacent to a lung fissure, most likely represents a lymph node and does not require subsequent monitoring with CT scans (Figure, B).[13] Satellite nodules, defined as small solid nodules surrounding a larger nodule, with nearby adenopathy may suggest a granulomatous infection (Figure, C). Fat density within the nodule is suggestive of a hamartoma (Figure, D), and vessels leading into (feeding) and exiting from (draining) the nodule can be seen with an arteriovenous malformation (Figure, E).

Evaluation of an individual with a pulmonary nodule requires knowledge about the factors associated with the probability that the nodule is malignant, the performance characteristics of additional testing, and the advantages and disadvantages of less intensive or more intensive follow-up (**Box 1**). Recognizing that the probability of malignancy and the yield of available diagnostic tests vary with the size and character of the nodule, nodules are often considered and managed by categorizing them into 1 of 3 groups: small solid nodules, larger solid nodules, and subsolid nodules.

Small Solid Pulmonary Nodules (<8 mm)
When incidentally discovered on imaging in individuals without a known history of malignancy, or when detected during LDCT screening, the probability of malignancy is very low. In the National Lung Screening Trial of 26 309 people at high risk for having lung cancer who received an LDCT, pulmonary nodules 4 to 6 mm in diameter accounted for 52.3% (3668 of 7019) of all nodules 4 mm or larger and had a 0.5% probability of malignancy, while nodules

Table 1. Society Guidelines for the Management of Pulmonary Nodules

Nodule diameter	American College of Chest Physicians[15a]	Fleischner Society[14a]	Lung-RADS[16b]
Up to 6 mm	≤4 mm: Low-risk: patient discussion, optional follow-up High-risk: follow-up CT scan at 12 mo (if stable no further follow-up) >4 to 6 mm: Low-risk: follow-up CT scan at 12 mo (if stable, no further follow-up) High-risk: follow-up CT scan at 6-12 mo (if stable, follow-up at 18-24 mo)	<6 mm/<100 mm³: Low-risk: No follow-up High-risk: Optional follow-up CT in 12 mo	<6 mm at baseline (or new nodule <4 mm on follow-up): return to annual screening (category 2)
6 to 8 mm	>6 to <8 mm: Low-risk: follow-up CT scan at 6-12 mo (if stable, follow-up at 18-24 mo) High-risk: follow-up CT scan 3-6 mo (if stable, then 9-12 mo and 24 mo)	6 mm to 8 mm/100 mm³ to 250 mm³: Low-risk: follow-up CT in 6-12 mo, then consider follow-up scan at 18-24 mo High-risk: follow-up CT in 6-12 mo, then repeat scan in 18-24 mo	≥6 mm to <8 mm at baseline (or new nodule 4 mm to <6 mm on follow-up): LDCT in 6 mo (category 3)
8 mm or greater	≥8 mm: Assess surgical risk and determine pretest probability of malignancy: Pretest probability <5%: surveillance CT in 3 mo Pretest probability 5%-65%: PET/CT scan to determine continued surveillance, nonsurgical biopsy, or surgical biopsy/resection Pretest probability >65%: referral for surgical biopsy or resection after appropriate staging workup	8 mm/>250 mm³: Low-risk: consider follow-up CT at 3 mo, PET/CT, or tissue sampling High-risk: consider follow-up CT at 3 mo, PET/CT, or tissue sampling	≥8 mm to <15 mm at baseline (or growing <8 mm or new nodule 6 mm to <8 mm on follow-up): 3-mo LDCT or PET/CT (category 4A) ≥15 mm (new or growing ≥8 mm): CT, PET/CT, and/or tissue sampling depending on probability of malignancy and comorbidities (category 4B)

Abbreviations: CT, computed tomography; LDCT, low-dose CT; PET, positron emission tomography.

[a] The American College of Chest Physicians criteria for low risk include individuals of younger age, little or no smoking history, smaller nodule size, regular margins, and location other than upper lobe. Criteria for high risk include individuals of older age, heavy smoking history, larger nodule size, irregular or spiculated margins, and upper lobe locations. Intermediate-risk individuals have a combination of high- and low-risk criteria. The Fleischner Society uses the same risk stratification as the American College of Chest Physicians.

[b] Guideline is used for management of screen-detected pulmonary nodules as part of lung cancer screening program. The Lung-RADS guideline categorizes nodules based on their risk of malignancy: category 1 is a CT without any nodules; category 2 nodules have an average probability of malignancy <1%; category 3 nodules have an average probability of malignancy of 1%-2%; category 4A nodules, 5-15%; and category 4B >15%.

7 mm to 10 mm in diameter accounted for 30.1% (2115 of 7019) of all nodules 4 mm or larger and had a 1.7% probability of malignancy.[9] However, these probabilities represented means among all individuals who present with a nodule in these size ranges. The probability of malignancy in an individual with lung cancer risk factors who has a 7-mm pulmonary nodule with concerning imaging features (ie, irregular or spiculated edges, upper lobe location) may approach 10%.

[18]F-fludeoxyglucose–positron emission tomography (FDG-PET) imaging, bronchoscopy, and transthoracic needle biopsy are unlikely to help identify malignancy in individuals with small solid pulmonary nodules. Nodules smaller than 8 mm in diameter are below the spatial resolution of FDG-PET imaging and are difficult to locate during bronchoscopic or transthoracic needle biopsy. For these reasons, individuals with pulmonary nodules smaller than 8 mm in diameter are usually monitored with serial chest CT imaging. The time interval between CT scans, performed to monitor changes in the nodule that could indicate malignancy, is based on the nodule size and the presence of risk factors for lung cancer. More recently published guidelines recommend longer intervals, such as 6 or 12 months, rather than 3 months, between monitoring scans.[14]

In summary, available guidelines suggest that a nodule smaller than 6 mm should be monitored with a chest CT in 12 months in individuals with lung cancer risk factors such as a history of smoking or a family history of lung cancer. No additional CT imaging is required in those without lung cancer risk factors (Box 1). A nodule between 6 mm and 8 mm should be monitored with a chest CT in 6 months. Flexibility in these time intervals (eg, 3-6 months, 6-12 months) is included in the guidelines to accommodate nodule features other than size, as well as clinician and patient preferences. Low radiation dose techniques are suggested for CT imaging. Details of the guideline recommendations for management of small solid pulmonary nodules can be found in Table 1.[14-16]

Larger Solid Pulmonary Nodules (≥8 to 30 mm)
The evaluation of larger solid nodules, 8 mm to 30 mm in diameter, involves consideration of patient and nodule characteristics, as well as an understanding of the diagnostic accuracy and safety of additional testing. The probability of malignancy in solid nodules of 8 mm to 30 mm ranges from very low (<1%) to high (>70%), depending on patient lung cancer risk factors and imaging features such as nodule size, location, edge features (eg, smooth, irregular, lobulated, or spiculated edges), and the presence of calcification. Available tests, such as FDG-PET/CT imaging, bronchoscopy, and transthoracic needle biopsy, have a higher diagnostic yield for nodules 8 mm to 30 mm in diameter than for small solid pulmonary nodules. Primary care clinicians should consider referring individuals with a pulmonary nodule of 8 mm to 30 mm in size to a multidisciplinary pulmonary nodule program if available (Box 1).

Risk Prediction | The evaluation of a larger solid pulmonary nodule (ie, 8-30 mm) should begin with an estimate of the probability that the nodule is malignant. This estimate can be based on an expert

Table 2. Validated Risk Prediction Models for Evaluation of Pulmonary Nodules

Risk prediction model	Mayo Clinic model[17]	Herder model[18]	VA model[19]	Brock University model[2]	Cleveland Clinic model[20]
Nodule detection	Incidental nodule on chest radiograph	Incidental nodule on chest radiograph and PET scan was performed for further evaluation	Incidental nodule seen on chest radiographic confirmed on CT imaging +/− PET scan	Nodules detected on LDCT as part of lung cancer screening program	Incidental nodules referred to biopsy or resection
% Of nodules that were malignant in the cohort used to develop the model	23	57	54	5.5	66.5
Model variables	Age Smoking history History of extrathoracic malignancy ≥5 y ago Nodule diameter Spiculation Upper lobe location	Mayo Clinic model + FDG-PET uptake	Age Smoking history Time since quitting smoking Nodule diameter	Age Sex Family history of lung cancer Emphysema Nodule Size Nodule type Location Nodule count	Age Smoking history Upper lobe location Solid and irregular/spiculated nodule edges Emphysema FDG-PET avidity History of cancer other than lung
Area under the curve	0.83	0.88	0.79	≥0.94	0.75-0.81 (C-index)

Abbreviations: CT, computed tomography; FDG, ^{18}F-fludeoxyglucose; LDCT, low-dose CT; PET, positron emission tomography; VA, Veterans Affairs.

clinician's assessment or may be calculated using a validated pulmonary nodule risk prediction calculator (Table 2). Variables in pulmonary nodule risk calculators include lung cancer risk factors (age, smoking history, personal history of other cancers, family history of lung cancer, presence of chronic obstructive pulmonary disease) and nodule features known to be associated with an increased probability of malignancy (larger size, upper lobe location, part-solid density, irregular or spiculated edges, fewer total pulmonary nodules, increased FDG uptake on PET imaging, or a concerning growth rate such as nodule volume doubling or diameter increasing by >25% in 30-400 days).

Several risk calculators have been developed and their accuracies have been externally validated (**Table 2**).[2,17-20] Individual risk calculators are more accurate in populations similar to those in which they were developed. For example, a risk calculator developed in a cohort of people with a pulmonary nodule presenting to a surgical clinic would not be as accurate when used to assess individuals with a pulmonary nodule identified during lung cancer screening. Thus, it is important to use a model that was derived from a population similar to the patient whose nodule is undergoing evaluation. A calculator developed in a screening population can be used to estimate the probability of malignancy in small solid pulmonary nodules as well. Many risk calculators have online tools to assist with their use. The clinical utility of pulmonary nodule risk calculators has been more difficult to confirm than their accuracy. Some studies have shown that the assessments of clinical experts and radiologists are comparable with that of the validated risk calculator scores (ie, area under the curve, 0.70-0.85 compared with 0.72-0.77, respectively, for identifying the presence of lung cancer).[21,22]

Management Options | In addition to the probability of malignancy, the evaluation of an individual with a larger solid pulmonary nodule is based on the yield of available diagnostic testing, patient comorbidities, and patient preferences. Management options for CT-detected pulmonary nodules include follow-up monitoring with serial CT imaging, further evaluation with FDG-PET imaging, nonsurgical biopsy (bronchoscopy, transthoracic needle biopsy), or surgical re-

section via a video or robotic-assisted approach. If a new nodule is first identified on a chest x-ray, a chest CT should be performed to better characterize the nodule and assess for lymphadenopathy.

Serial CT imaging is appropriate if a pulmonary nodule has a low probability of malignancy (eg, <10%), if other management options (FDG-PET imaging, bronchoscopic or transthoracic needle biopsy) are considered unlikely to be informative or are high-risk procedures, or if an informed patient prefers a less aggressive approach. For solid pulmonary nodules 8 mm to 30 mm in size, when surveillance chest CT is the preferred approach, the first surveillance chest CT should be performed 3 months after the initial CT. A meaningful change in nodule size is defined as an increase of 2 mm or more in mean diameter, rounded to the nearest millimeter.[23] If the nodule decreases in size, additional monitoring is not required. If the nodule remains stable in size, a chest CT should be performed 6 months later. If the nodule is unchanged on this subsequent imaging, a follow-up chest CT 12 months later would be appropriate. If the nodule is growing at a pace consistent with malignancy (eg, volume doubling time >30 days and <400 days), it should be further evaluated without delay (see options below). If the nodule grows at a very slow pace (eg, volume doubling time >400 days), an indolent malignancy remains possible and a discussion with the patient about the management strategy should occur.

FDG-PET imaging can assist with characterization of an intermediate-risk large solid pulmonary nodule (eg, 10%-70% probability of malignancy). FDG-PET imaging provides information about the metabolic activity of the nodule. A pulmonary nodule with high metabolic activity is more likely to be malignant, although there is significant overlap in FDG uptake between malignant and benign (ie, infectious/inflammatory) nodules. An indolent malignancy can have a false-negative result given its lower metabolic activity. A meta-analysis evaluating the discriminative accuracy of FDG-PET imaging for pulmonary nodule evaluation reported a pooled sensitivity of 89% (95% CI, 86%-91%) and specificity of 75% (95% CI, 71%-79%).[24] There was significant heterogeneity of the specificity, with lower specificity values identified in higher-quality studies and a 16% lower specificity in areas with endemic

fungal infections such as the Ohio River Valley (histoplasmosis) and Southwestern US (coccidioidomycosis).[24] FDG-PET imaging may also identify regional and distant spread of lung cancer.

When imaging findings suggest an intermediate probability of malignancy (eg, 10%-70%), a nonsurgical biopsy, such as a CT-guided transthoracic needle biopsy or guided bronchoscopy, may be offered. The choice between a CT-guided transthoracic needle biopsy and a guided bronchoscopy procedure is based on several factors, including location of the nodule, available clinical expertise, and patient comorbidities and values. A pulmonary nodule located in the periphery of the lung field is more likely to be accessible by transthoracic needle biopsy, while a pulmonary nodule located along the path of an airway may be more easily approached by bronchoscopy. In a meta-analysis, transthoracic needle biopsy had a higher pooled diagnostic yield (93% [95% CI, 90%-96%]) than bronchoscopy (75% [95% CI, 69%-80%]), but was associated with an increased risk for pneumothorax (26%) and hemorrhage (16%).[25] Advances in technologies that augment the ability to guide the bronchoscope to a peripheral nodule, confirm the location of the nodule, and provide representative samples of the nodule, including electromagnetic navigation,[26] radial endobronchial ultrasound, ultrathin bronchoscopes,[27] and robotic-assisted bronchoscopy,[28] have substantially improved diagnostic yields of guided bronchoscopy while maintaining low complication rates. In a meta-analysis, the pooled sensitivity for malignancy of electromagnetic navigation bronchoscopy was 77% (95% CI, 72%-82%) with a 2.0% risk of pneumothorax (95% CI, 1.0%-3.0%) and 0.8% risk of major bleeding (95% CI, 0.5%-1.1%).[29] An added value of performing bronchoscopy is the ability to perform endobronchial ultrasound-guided biopsy of the hila and mediastinum if indicated for staging.

When the probability of malignancy is high (eg, >70%), proceeding to surgical resection via a video or robotic-assisted approach is recommended in individuals without life-limiting comorbidities, such as severe emphysema or severe heart failure, and who meet criteria of cardiopulmonary fitness, such as predicted postoperative forced expiratory volume in 1 second and diffusing capacity greater than 60% predicted, suggesting a low risk associated with surgical resection.[30] Ideally, a surgical wedge resection to confirm the presence of cancer, obtained during an intraoperative frozen section, can be followed by definitive treatment (eg, lobectomy or segmentectomy) during the same operation. For individuals with life-limiting comorbidities and for those at high risk for complications from surgical resection, other potential nonsurgical options may include nonsurgical biopsy (transthoracic needle biopsy and bronchoscopy), stereotactic radiotherapy, or other ablative therapies. Feasibility of the biopsy, patient fitness, and patient preferences help inform this decision-making process.

Individualizing Care | In general, nodules can be classified into 1 of 3 categories of risk of malignancy and managed accordingly: those with a low risk (eg, <10%) can be monitored with imaging; those with an intermediate risk (eg, 10%-70% risk) should typically undergo additional diagnostic testing, and those with a high risk (eg, >70% risk) should proceed directly to surgery. These thresholds refer to the management of the population of patients with a pulmonary nodule and need to be considered in the context of other factors for individual patients. Two nodules with an identical

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Box 2. Individualized Pulmonary Nodule Management Based on Probability of Malignancy[14-16,31-33a]

<1% No additional testing or monitoring needed.

1%-5% Monitoring with chest computed tomography (CT) per guideline recommendations, based on nodule size.

5%-30% Monitor with chest CT in 3 months or pursue additional testing with positron emission tomography (PET)/CT imaging and/or a nonsurgical biopsy. Factors that favor monitoring include severe comorbidities, limited life expectancy, difficult nodule location, patient favors conservative management, slow growth rate, and low metabolic activity.

30%-65% Additional testing with PET/CT imaging and/or a nonsurgical biopsy. Factors that favor guided bronchoscopy vs transthoracic needle biopsy include airway leading to the nodule, severe emphysema, available local expertise, and need to invasively stage the mediastinum.

65%-90% Additional testing with PET/CT imaging and/or a nonsurgical biopsy or proceed directly to thoracoscopic surgical resection. Factors that favor surgical resection include low-yield nonsurgical biopsy location, excellent cardiopulmonary fitness, and patient favors aggressive management.

>90% Thoracoscopic surgical resection or stereotactic radiotherapy based on patient comorbidities and values.

[a] Probability of malignancy is estimated based on clinical experience or a validated risk prediction calculator.

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probability of malignancy may be managed differently. Factors that influence clinical decisions include the anticipated diagnostic yield of a nonsurgical biopsy, patient comorbidities that influence the safety of a procedure, the likelihood of benefit from establishing a diagnosis (life expectancy, nodule growth rate, metabolic activity), and patient values (**Box 2**). It is important to note that after completion of all nonsurgical testing (ie, FDG/PET imaging, nonsurgical biopsy), in some patients the probability of malignancy may be higher than accepted thresholds for monitoring with imaging and lower than accepted thresholds for surgical resection. In this situation, the managing clinician and patient should discuss the tradeoffs of monitoring vs surgical resection to determine the most appropriate next step for that individual. It is also important to recognize that some cancers may grow slowly on serial imaging, providing the opportunity for the clinician and patient to discuss the preferred timing of treatment.

Subsolid Pulmonary Nodules
Subsolid pulmonary nodules consist of pure ground-glass (Figure, F) and part-solid pulmonary nodules. Ground glass refers to a density in which the lung architecture (such as blood vessels) is not obscured by the nodule. Part-solid refers to a nodule that has both ground-glass and solid components. Malignant subsolid pulmonary nodules grow at a slower pace than malignant solid nodules and are typically adenocarcinomas (adenocarcinoma in situ or minimally invasive adenocarcinoma in the ground-glass portion and invasive adenocarcinoma in the solid portion). In 1 series of 439 pure ground-glass nodules that were smaller than 6 mm in diameter and followed up for at least 5 years (median imaging follow-up, 6.0 years), 45 (10.3%) grew and 4 (0.9%) developed into adenocarcinomas.[34] In another series of 226 patients with subsolid pulmonary nodules,

Table 3. Society Guidelines for the Management of Subsolid Pulmonary Nodules

American College of Chest Physicians[15]	Fleischner Society[14]	Lung-RADS[16a]
≤5 mm: no follow-up	<6 mm/<100 mm³: Ground-glass nodule: no routine follow-up Part-solid: no routine follow-up	Ground glass nodule <30 mm at baseline (or any size unchanged): return to annual screening (category 2)
		Part-solid nodule <6 mm at baseline: return to annual screening (category 2)
		Part-solid nodule <6 mm (new): follow-up CT scan at 6 mo (category 3)
>5 mm: Ground-glass nodule: follow-up CT scan at 12 mo then annual through 3 y Part-solid nodule: ≤8 mm solid component: follow-up CT scan at 3, 12, and 24 mo then annual until 5 y >8 mm solid component: follow-up CT scan at 3 mo, further evaluation with PET, nonsurgical biopsy, and/or resection if persists	≥6 mm/>100 mm³: Ground-glass nodule: follow-up CT scan 6-12 mo then every 2-5 y Part-solid nodule: follow-up CT scan 3-6 mo then annually for 5 y	Ground glass nodule ≥30 mm at baseline or new on follow-up: follow-up 6-mo CT (category 3) Part-solid nodule: Solid component <6 mm: follow-up CT at 6 mo (category 3) Solid component ≥6 to <8 mm or new or growing and <4 mm: follow-up CT at 3 mo (category 4A) Solid component ≥8 mm or new or growing and ≥4 mm: further evaluation (category 4B)

Abbreviations: CT, computed tomography; PET, positron emission tomography.

a Guideline is used for management of screen-detected pulmonary nodules as part of lung cancer screening program.

invasive cancer was identified in 4.1% (3 of 74) of resected pure ground-glass malignant nodules (median diameter at time of detection, 10 mm), 70.0% (14 of 20) with a solid component greater than 25% of the total nodule size, and 45.5% (10 of 22) of those with growth in the solid component.[35] A summary of 24 case series that included 704 patients reported that the 5-year lung cancer–specific survival rate was 100% for malignant pure ground-glass nodules with a mean tumor size of 7.9 mm to 16.6 mm.[36]

Malignant subsolid pulmonary nodules are relatively slow growing compared with malignant solid nodules. In the series described above of 226 patients with subsolid pulmonary nodules, the solid component of a malignant part-solid nodule grew in 100% (17 of 17) of nodules within the first 3 years of monitoring, and in 86.4% (19 of 22) of malignant pure ground-glass nodules, but none of these cancers spread beyond the nodule during this follow-up period.[35] The metabolic activity of a malignant subsolid pulmonary nodule is relatively low (positive FDG-PET scan in 60%)[37] and the yield of transthoracic needle biopsies is also relatively low (51.2%).[37,38] These findings suggest that longer periods of imaging surveillance may be appropriate when following up patients with pure ground-glass nodules, particularly in people with advanced age or with comorbid conditions whose life expectancy is lower than in people who are younger or without comorbid conditions.

In summary, current guidelines suggest a pure ground-glass nodule smaller than 6 mm in diameter does not require additional testing or monitoring, but patients and clinicians may decide to perform additional testing or monitoring in selected situations. A ground-glass nodule 6 mm or larger can be followed with a chest CT in 6 to 12 months followed by every 2 years for 5 years if it remains stable. The management of a part-solid nodule should be based on the size of the solid component. Surveillance with a chest CT should occur in 6 months if the solid component is smaller than 6 mm or in 3 months if the solid component is 6 mm to 8 mm. Management of a part-solid nodule in which the solid component is 8 mm or larger should follow the recommended guidance for large solid nodules.[16,17] When monitoring a subsolid pulmonary nodule, the development or growth of a solid component of the nodule is a concerning finding that should lead to more frequent surveillance imaging, nonsurgical biopsy, or surgical resection based on the size of the solid component of the nodule. Growth of the ground-glass component alone does not suggest a malignancy has become invasive and thus does not require more intensive or invasive management. FDG-PET imaging is not useful for evaluating the probability of malignancy unless a solid component of at least 8 mm is present. Minimally invasive sublobar resection may be considered without biopsy when the size of the solid component of a subsolid lung nodule is growing and is 8 mm or larger (**Table 3** and **Box 1**).[14-16]

Guidelines

Several societies have developed guidelines to assist with the evaluation of an individual with a pulmonary nodule.[14-16,31-33] These guidelines vary in their scope and focus, and some are specific to certain geographic regions and health systems.[32,33] Some of these guidelines focus on management of a small incidentally detected pulmonary nodule, others focus on management of an LDCT screen-detected pulmonary nodule, and some focus on both types of nodules. However, all the guidelines are organized based on an estimate of the probability that a pulmonary nodule is malignant, knowledge of the risk of malignancy in nodules of different densities, and workup for further assessment of the nodule. Differences in guideline recommendations include the use of different thresholds for the probability of malignancy to provide management recommendations (eg, <5%, 10%, or 15% probability for monitoring for nodule growth, 5%-15% to 65%-70% for additional nonsurgical evaluation, and >65% or >70% for surgical resection), the frequency and duration of image-based monitoring, the preferred risk calculators for identifying likelihood of malignancy, and whether volumetric imaging with growth rate calculation is recommended.

Guideline recommendations have changed over time, based on a better understanding of probability of malignancy and growth patterns of malignant pulmonary nodules. Changes have included using a higher threshold for probability of malignancy, compared with past guidelines, for use of imaging to monitor growth of a nodule (eg, <15% probability currently compared with <5% probability in the past), monitoring less frequently and for shorter durations, and allowing more flexibility in frequency of diagnostic testing, to accommodate consideration of patient risk factors, comorbidities, and values. These guidelines refer to an incidentally or screen-detected pulmonary nodule and not a pulmonary nodule in an individual with a known malignancy for whom metastatic disease is a concern (Box 1). Pulmonary nodule guideline recommendations are summarized in Table 1 and Table 3.

Compliance of clinicians with guideline recommendations and patients' actual follow-up in practice may be suboptimal. In 1 study

of 197 patients with pulmonary nodules, 88 (44.7%) received care inconsistent with guidelines (eg, next surveillance imaging prior to or after the interval recommended in the guidelines, a nonsurgical biopsy instead of surveillance imaging).[39] Features leading to non-compliance include inappropriate radiologist guidance (65.6% vs 10.8%; overevaluation relative risk [RR], 4.6 [95% CI, 2.3-9.2]; underevaluation RR, 4.3 [95% CI, 2.7-6.8]), receiving care at more than 1 facility (RR, 2.0 [95% CI, 1.5-2.7]), and nodule detection during an inpatient stay or preoperative visit (RR, 1.6 [95% CI, 1.1-2.5]).[39] Features associated with compliance with following guideline management recommendations by clinicians and compliance with care recommendations by patients include patient distress (64.4% vs 57.4%),[40] point-of-care reference materials provided in the emergency department (80.2% vs 67.5%),[41] clinical decision support tools at workstations (65.2% vs 49.6%),[42] guideline templates added to radiology reports (45% vs 31%),[43] and high-quality communication (OR, 3.7 [95% CI, 1.3-10.6]).[40]

System of Care

In practice, primary care clinicians must counsel patients about the evaluation and diagnostic testing of pulmonary nodules and monitor timing of follow-up diagnostic testing.

Multidisciplinary pulmonary nodule specialty clinics are available in some regions to assist in the treatment of patients with pulmonary nodules. These clinics, comprised of a multidisciplinary team of nodule management experts (eg, pulmonologists, thoracic surgeons, radiologists), identify patients with pulmonary nodules by flagging radiology reports (either manually or through computational linguistics) when a pulmonary nodule is identified on imaging. Clinicians at these clinics communicate directly with patients to inform them of the results, use guideline-based pulmonary nodule management algorithms and health management systems to ensure adherence to appropriate follow-up testing, and provide automated patient reminders. In a series of 113 patients, care followed guideline recommendations in 76 patients (67.2%), with the highest rates (88% concordant) observed in those with malignant nodules.[44] In this setting, among 5057 individuals in which 1863 (37%) received less intensive evaluation than recommended in guidelines, fewer procedure-related adverse events (risk difference, −5.9%), lower radiation exposure (−9.5 mSv), and lower expenditures (−$10 916) were noted, without affecting the stage of cancer at diagnosis (risk difference, 4.6%).[45] These results may suggest that individualizing care in a multidisciplinary pulmonary nodule clinic could yield favorable outcomes.

Shared Decision-making

In a study of 121 patients with pulmonary nodules, psychological distress about the presence of a pulmonary nodule was reported by 69 patients (57.0%), with 25% reporting continued distress 2 years after a pulmonary nodule was diagnosed.[46] Fifty-five patients (45.5%) estimated the risk of malignancy associated with their pulmonary

nodule to be at least 30% when the calculated average risk was 10%.[46] High-quality communication from clinicians has been associated with less patient distress. No distress after a pulmonary nodule diagnosis was reported in 60.3% of patients who received high-quality communication compared with 40.7% in those who received low-quality communication.[47] In 316 clinician encounters regarding management of pulmonary nodules in which decision-making occurred, patients preferred to have an active role in the management of their pulmonary nodule in 313 (98%) of the encounters. However, only one-half of clinicians reported engaging in shared decision-making with patients diagnosed with a pulmonary nodule.[48] Clinicians with more years of experience and those who reported feeling more comfortable evaluating a pulmonary nodule used shared decision-making more often.[48]

Future Directions

Large imaging data sets have supported the application of artificial intelligence to identify pulmonary nodules most likely to be malignant. A convolutional neural network trained on more than 15 000 images from the National Lung Screening Trial showed improved classification over available risk prediction models when externally validated (area under the curve, 0.84-0.92 vs 0.78-0.82).[49] Several molecular biomarkers have been developed to improve pulmonary nodule risk prediction. Some of these biomarkers, present in the blood, airway epithelium, and breath, evaluate changes in circulating tumor DNA, mRNA expression, proteins, autoantibodies, or metabolites, and are currently undergoing assessment for clinical utility.[50,51] Multidisciplinary programs of care for individuals with a pulmonary nodule, described above, are increasing in number. Population management tools, which may include decision support tools and may help people adhere to recommended follow-up diagnostic testing, are also increasingly available. These programs may improve clinician adherence with guideline recommendations, patient adherence with recommended management, communication, and patient-related outcomes.

Limitations

This review has several limitations. First, for some covered topics, high-quality data were not available. Second, some relevant articles may have been missed. Third, a formal quality assessment of included articles was not performed.

Conclusions

Pulmonary nodules are identified in approximately 1.6 million people per year in the US and approximately 30% of chest CT images. The treatment of an individual with a pulmonary nodule should be guided by the probability that the nodule is malignant, safety of testing, the likelihood that additional testing will be informative, and patient preferences.

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