A practical diagnostic algorithm for approaching the solitary pulmonary nodule (SPN), stratifying clinical risk factors in a standardized manner and blending this information with radiologic clues, would point the physician toward a benign or malignant cause. Such an approach would be expected to spare patients with benign causes the morbidity and cost associated with invasive tissue sampling and, at the same time, guide the physician toward recommending invasive tests for the nodules likely to be malignant.

Calculation of Pretest Probability

The clinical and radiologic features described in Part 1 (see page 825) can individually provide clues as to whether a given SPN is benign or malignant. However, assimilating all these factors and assigning the “weight” of probability of malignancy to each factor, and coming up with the approximate probability of malignancy, is an onerous task. Let us take, for example, a 65-year-old patient with a 20-pack-year smoking history who is found to have a 3-cm noncalcified SPN with lobulated borders in the right upper lobe (Fig 1). The physician is faced with the task of calculating the probability of malignancy in this nodule. If the probability is low, the physician is likely to recommend follow-up of this SPN with serial CT scans. On the other hand, if the probability of malignancy is moderate or high, the patient should be referred for further testing or tissue sampling. How consistent are physicians in stratifying the malignant potential of a SPN? In the instance cited, the range of pretest probability was calculated by showing the same image on the same computer screen to 44 physicians (internists and pulmonologists in academic and private practice).
in a community hospital in New York). The range was found to be 2% to 95% (unpublished data). Although experienced physicians routinely make these judgments by gestalt in day-to-day practice, standardized methods have been developed to calculate the probability of the malignancy of a SPN.\textsuperscript{17}

Bayesian analysis is one such approach. Likelihood ratios for malignancy are assigned to each clinical and radiologic feature by dividing the probability of finding a particular feature in patients with malignant nodules by the probability of finding the same feature in patients with benign nodules. The odds of malignancy can then be calculated by multiplying the likelihood ratios for each individual clinical and radiologic feature by the prior odds of malignancy. Probability of malignancy can then be calculated easily from the odds. A number of authors developed this approach during the 1970s and 1980s,\textsuperscript{18-23} but Gurney et al\textsuperscript{24,25} provided the most rigorous test. They derived likelihood ratios from a database of 3,858 patients and then validated the model by comparing it with subjective clinical assessments. Following a review of the literature current at that time, they calculated likelihood ratios for age, smoking history, history of previous malignancy, hemoptysis, size of the SPN, location, edge characteristics, calcification, growth rate, and cavity wall thickness. Needless to say, these calculations were only as accurate as the studies that were used to glean the data. Subsequently, a total of 66 patients with SPNs were evaluated for the probability of malignancy by four radiologists with an average experience of 16 years, yielding an accuracy of 62.5% and an error rate of 37%. When the previously determined Bayesian analysis was employed by a separate set of radiologists with far less experience, the accuracy and error rates were much better, at 77.5% and 15.5% respectively, with fewer false-negative results.

A convenient and reliable way of performing this assessment is by using a calculator available online at www.chestx-ray.com under the tab “Practice.” This calculator takes into account the likelihood ratios from a list of clinical and radiologic factors (Table 1) and generates a percentage probability of malignancy. Based on this calculator, the pretest probability of malignancy in the lesion described in the previous paragraph is 95%. Interestingly, only 66% of the respondents in our survey correctly identified the pretest probability of malignancy as ≥ 60%.

Swensen et al\textsuperscript{26} employed multivariate regression analysis in an attempt to account for the correlation and interaction among various clinical and radiologic risk factors. They derived their model from a cohort of 419 patients with SPNs detected on chest radiograph and identified risk factors as delineated in Table 1. This prediction model is described by the following equation:

\[
\text{Probability of malignancy} = e^{\frac{x}{1+e^x}}
\]

\[
x = -6.8272 + (0.0391 \times \text{age}) + (0.7917 \times \text{smoke}) \\
+ (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) \\
+ (1.0407 \times \text{spiculation}) + (0.7838 \times \text{location})
\]

where \(e\) is the natural logarithm, age is the patient’s age in years, smoke = 1 if the patient is a current or former smoker (otherwise, smoke = 0), diameter is the diameter of the nodule in millimeters, spiculation = 1 if the edge of the nodule has spicules (otherwise, spiculation = 0), and location = 1 if the nodule is located in an upper lobe (otherwise, location = 0). The model

Table 1—Calculation of Probability of Malignancy

<table>
<thead>
<tr>
<th>Source/Reference</th>
<th>Factors Taken Into Consideration to Determine the Probability of Malignancy</th>
</tr>
</thead>
</table>
| www.chestx-ray.com | 1. Age  \\
|                   | 2. Smoking (ever vs never and pack-y)  \\
|                   | 3. Hemoptysis  \\
|                   | 4. History of prior malignancy  \\
|                   | 5. Nodule diameter  \\
|                   | 6. Location  \\
|                   | 7. Edge characteristics  \\
|                   | 8. Growth rate  \\
|                   | 9. Cavity wall thickness  \\
|                   | 10. Calcification  \\
|                   | 11. Contrast enhancement on CT scan > 15 HU  \\
|                   | 12. PET scan |
| Swensen et al\textsuperscript{26} | 1. Age  \\
| | 2. Smoking history (ever vs never)  \\
| | 3. History of previous malignancy > 5 y ago  \\
| | 4. Presence of spiculation  \\
| | 5. Upper lobe location |
| Gould et al\textsuperscript{27} | 1. Age  \\
| | 2. Smoking history (ever vs never)  \\
| | 3. Nodule diameter  \\
| | 4. Time since quitting smoking |

HU = Hounsfield unit.
was then validated on separate groups of patients showing excellent calibration of the prediction model.20,28 Additionally, the area under the curve of the prediction model was not statistically different from PET scan results. These scan results, when added to the predicted probability calculated by the model, improved the area under the curve by 13.6% (95% CI, 6.21; P = .0003). Although this “Mayo Clinic model” yielded an excellent receiver-operating characteristic curve (0.8328 ± 0.0226), it had several important limitations: (1) Patients who had been given a diagnosis of any cancer, including lung cancer, in the past 5 years were excluded (as discussed previously, a history of malignancy confers a significant risk of a new SPN being malignant, whether metastatic or a new lung primary, and excluding these patients from the calculation would therefore potentially underestimate the probability of malignancy); (2) the model was developed in a cohort of patients with lung nodules who were originally managed more than 20 years previously at a single tertiary care center in the midwestern United States, thereby limiting the model’s generalizability; and (3) the prevalence of malignancy was relatively low (23%), and in 12% of patients a final diagnosis was not determined.

To address these limitations, Gould et al27 studied a geographically diverse sample of 375 veterans with a high prevalence of malignant SPNs (54%). This study again identified independent predictors of malignancy by using multivariate regression analysis (Table 1). Interestingly, upper lobe location was not found to be an independent predictor of malignancy. Notable limitations to this “VA model” are as follows: (1) SPN < 7 mm in diameter were excluded from the study; (2) the study sample consisted primarily of older white men, thereby limiting the generalizability of the model to female patients and patients of other ethnicities; (3) information about nodule morphology on CT chest scans was not taken into account (instead of definitive nodule morphology characteristics, radiologists were asked to rate each SPN on a five-point scale between “definitely benign” and “definitely malignant” based on chest roentgenogram morphology; this characterization was taken as a surrogate marker for spiculation. A “definitely malignant” nodule morphology on chest roentgenogram did not attain statistical significance as an independent predictor for malignancy, possibly because of the limited resolution of the chest roentgenogram images. A spiculated nodule should, thus, be considered “high probability” for malignancy even if the pretest probability calculated by the “VA model” suggests otherwise); and (4) the model may not be well calibrated for use in populations in which the prevalence of malignancy is much lower or higher than in this study. Physicians would therefore have to carefully consider the prevalence of malignancy in their practice setting when choosing between the two models. A comparison of these two models in a sample of 151 patients with SPNs 7 to 30 mm in size demonstrated no statistically significant difference in the receiver-operating characteristic curves, suggesting that both models were sufficiently accurate to guide clinical decision making in patients with SPNs.15

Regardless of the model used, an assessment must then be made as to whether the calculated pretest probability of malignancy is sufficient to guide clinical decision-making (the “observe vs excise” dilemma presented in the previous example), or whether further imaging studies are needed to give a clearer picture as to the probability of malignancy. These imaging studies are discussed in the following sections.

**Practical Algorithmic Approach to the SPN**

To consolidate the preceding discussion into a logical sequence of steps, we propose a practical algorithm for approaching a SPN (Fig 2) detected on chest roentgenogram or CT chest scan.

**Step 1**

The first step in the evaluation of a SPN detected on chest roentgenogram is to review a previous chest roentgenogram or CT scan to assess the growth rate. A volume doubling time ≥ 2 years or a benign pattern of calcification suggests the SPN is benign and requires no further workup. However, one should be cognizant that a malignant subsolid nodule may have a doubling time ≥ 2 years, as mentioned earlier.

**Step 2**

The second step is to decide whether the SPN is solid or subsolid. A CT chest scan with thin sections through the nodule is strongly recommended for precise characterization of the lesions. Consideration should be given to the use of low-dose techniques for this purpose as well as for all subsequent follow-up CT examinations when needed.

**Step 3**

Evaluation of solid nodules is discussed in algorithm 2. See Figure 3 for details.

**Step 4**

Subsolid nodules are an exception to the volume doubling rule, and are discussed separately in algorithm 3. See Figure 4 for details.
EVALUATION OF THE SOLID SPN

**Step 5**
A solid SPN of ≤ 8 mm in diameter, given a low pretest probability, can be followed as per the recommendations of the Fleischner Society.9

**Step 6**
A solid SPN > 8 mm in diameter would require an assessment of the pretest probability of lung cancer, keeping in mind the clinical and morphologic considerations elaborated on previously.

**Step 7**
If the pretest probability of malignancy is calculated to be very low (arbitrarily < 5%), serial observation as per the Fleischner Society recommendations is adequate.

**Step 8**
If the calculated pretest probability of malignancy is high (arbitrarily > 60%), the patient should proceed directly to tissue diagnosis if clinically feasible (without unacceptably high risk) and in accordance with the patient’s preference. Transthoracic needle aspiration, transbronchial biopsy with or without electromagnetic navigation technology, or surgical biopsy by video-assisted thoracoscopic surgery may be employed, based on the size and location of the SPN. The choice of diagnostic modality must be center specific and physician specific; peripheral lesions are often easily accessible in a center with strong interventional radiology; whereas centers that use advanced bronchoscopic techniques may prefer navigational bronchoscopy for amenable peripheral lesions. Other centers may prefer a surgical diagnostic modality; in such an instance, a PET scan may be useful for preoperative staging and may help the surgeon decide which areas to biopsy. Lack of uptake on PET scan would not be a reason to defer tissue sampling.

**Step 9**
For the “intermediate” range of risk (5%-60%), the judicious use of an 18F-2-deoxy-2-fluoro-d-glucose (FDG)-PET scan should be made, with an integrated PET-CT scan used whenever possible. The sensitivity and specificity of the FDG-PET scan in detecting malignancy in a SPN, or indirectly suggesting malignancy via mediastinal lymph node involvement or distant metastases, are high enough to warrant a tissue diagnosis, if the test is positive. Solid SPNs with negative PET scans can be followed with serial CT chest scans according to the American College of Chest Physicians evidence-based clinical guidelines (3, 6, 12, and 24 months).29
**Evaluation of Subsolid SPN**

**Step 5**
In the event that the initial CT chest scan reveals a subsolid SPN, a different approach is warranted, which we have modified from Godoy and Naidich\(^{10}\) and the recent Fleischner Society guideline.\(^{31}\) For the subsolid nodule, the initial step is to determine whether the SPN is a pure ground glass nodule (GGN), or a mixture of ground-glass and solid components.

**Step 6**
Controversy surrounds the management of subsolid nodules because of a paucity of data. Various expert opinions exist in the literature but the consensus is that the SPN be managed conservatively.

Pure GGNs ≤ 5 mm in size do not require further follow-up. Pure GGNs > 5 mm in size should be followed with a repeat CT chest scan in 3 months to ascertain if the lesions have resolved spontaneously. A case-by-case evaluation must then be made regarding the decision for invasive tissue biopsy if the SPN persists. If the lesion has not changed in size, conservative management is recommended, with at least three consecutive annual thin-section CT scans required to document stability.

Although data to support an optimal duration of conservative follow-up are lacking, the follow-up period of 3 years takes into consideration the slow doubling times of adenocarcinomas. Accurate assessment of interval change in the size of these nodules is best accomplished by comparing thin-section CT scans,
may minimize the interobserver variability in estimating the risk of malignancy and may, in turn, steer the physician to more strategic management pathways. The algorithmic approach begins by separating subsolid from solid nodules. For SPNs 8 mm in size and for those 8 mm in size with a low probability of malignancy, serial CT scans are recommended (Fleischner Society and American College of Chest Physicians guidelines, respectively). The high-risk SPN 8 mm in size should be resected or should undergo tissue diagnosis; obviously, patient preference and the severity of comorbid medical conditions must be considered prior to any intervention.

An integrated FDG-PET scan should be considered for a SPN with an intermediate risk of malignancy. If activity is picked up on the FDG-PET scan, the nodule should be resected. On the other hand, a pure GGN 5 mm in diameter does not require further workup. Those 5 mm require serial CT scans for a duration 2 years. And finally, subsolid GGNs 5 mm that persist beyond 3 months should undergo PET-CT scan or be considered for surgical resection. Although many questions remain at this time, we hope this practical algorithmic approach to evaluating these nodules and by closely monitoring any change in the attenuation of lesions. Either change should be interpreted as indicative of possible malignancy, and in most cases, surgical resection should be strongly considered. PET-CT scanning is not of adequate diagnostic value, either for differentiating benign from either premalignant or invasive lesions or for staging malignant lesions, and is, therefore, best avoided in this setting. Finally, SPNs with mixed solid and ground-glass components of any size represent malignancy often enough to warrant close observation. A PET-CT scan may be considered at this stage, especially if the solid component is >8 mm in diameter. Based upon the results of this test, biopsy, surgical resection, or surveillance with serial CT scans may be performed. It is important to point out that if the nodule changes in size or characteristics, the likelihood of malignancy is high and surgical resection should be contemplated.

CONCLUSION
In this article, we advocate calculating the pretest probability of malignancy in a SPN. Such a practice may minimize the interobserver variability in estimating the risk of malignancy and may, in turn, steer the physician to more strategic management pathways. The algorithmic approach begins by separating subsolid from solid nodules. For SPNs <8 mm in size and for those >8 mm in size with a low probability of malignancy, serial CT scans are recommended (Fleischner Society and American College of Chest Physicians guidelines, respectively). The high-risk SPN >8 mm in size should be resected or should undergo tissue diagnosis; obviously, patient preference and the severity of comorbid medical conditions must be considered prior to any intervention. An integrated FDG-PET scan should be considered for a SPN with an intermediate risk of malignancy. If activity is picked up on the FDG-PET scan, the nodule should be resected. On the other hand, a pure GGN ≤5 mm in diameter does not require further workup. Those >5 mm require serial CT scans for a duration >2 years. And finally, subsolid GGNs >5 mm that persist beyond 3 months should undergo PET-CT scan or be considered for surgical resection. Although many questions remain at this time, we hope this practical algorithmic approach to evaluating these nodules...
can help physicians navigate toward a definitive diagnosis in a timely, reliable, and resource-conscious fashion.

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**REFERENCES**