Background: Pulmonary nodules are frequently detected during diagnostic chest imaging and as a result of lung cancer screening. Current guidelines for their evaluation are largely based on low-quality evidence, and patients and clinicians could benefit from more research in this area.

Methods: In this research statement from the American Thoracic Society, a multidisciplinary group of clinicians, researchers, and patient advocates reviewed available evidence for pulmonary nodule evaluation, characterized six focus areas to direct future research efforts, and identified fundamental gaps in knowledge and strategies to address them. We did not use formal mechanisms to prioritize one research area over another or to achieve consensus.

Results: There was widespread agreement that novel tests (including novel imaging tests and biopsy techniques, biomarkers, and prognostic models) may improve diagnostic accuracy for identifying cancerous nodules. Before they are used in clinical practice, however, better evidence is needed to show that they improve more distal outcomes of importance to patients. In addition, the pace of research and the quality of clinical care would be improved by the development of registries that link demographic and nodule characteristics with patient-level outcomes. Methods to share data from registries are also necessary.

Conclusions: This statement may help researchers to develop impactful and innovative research projects and enable funders to better judge research proposals. We hope that it will accelerate the pace and increase the efficiency of discovery to improve the quality of care for patients with pulmonary nodules.

Contents
Overview
Introduction
Methods
Results
Framing Research Questions for Novel Diagnostic Procedures
Nodule Registries
Data Sharing
Diagnostic Imaging and Invasive Procedures
Biomarkers
Prediction and Prognostic Models
Emerging Treatments
Logistics and Implementation
Patient-centered Outcomes
Discussion
Limitations
Conclusions

Overview
Pulmonary nodules are frequently detected during diagnostic chest imaging and as a result of lung cancer screening. Current guidelines for their evaluation are largely based on low-quality evidence, and patients and clinicians could benefit from more research in this area.

In this research statement from the American Thoracic Society,
a multidisciplinary group of clinicians, researchers, and patient advocates reviewed available evidence for pulmonary nodule evaluation, characterized areas to direct future research efforts, and identified fundamental gaps in knowledge and strategies to address them.

We developed the following key recommendations:

- The efficacy and effectiveness of new diagnostic strategies (including novel imaging tests and biopsy techniques, biomarkers, and prognostic models) should be evaluated using established phases of test development, from identification of a novel strategy or characteristic to establishment of clinical utility.
- Registries that link demographic and nodule characteristics with patient-level outcomes should be developed.
- Pulmonary nodule evaluation strategies are guided by subsequent treatment options for early-stage lung cancer, and these treatments should be rigorously studied.
- Potential interventions and quality metrics to improve nodule evaluation processes should be studied before requiring their implementation.
- Tests and interventions should be evaluated for their impact on patient-centered outcomes.

This statement may help researchers develop impactful and innovative proposals and enable funders to better judge novel research efforts. Participants also identified several topics for discussion that came with a substantial drawback, as almost 40% of subjects had a positive screening test result during the three rounds of screening, mostly as a result of pulmonary nodule identification.

The majority of pulmonary nodules are benign, but the most worrisome cause of a pulmonary nodule is bronchogenic carcinoma. Because of the lethality of lung cancer, the difficulty of sampling small lesions for biopsy, and the relatively slow rate of growth even if the nodule is lung cancer, it is recommended that most patients with nodules undergo further evaluation (15–17). Patients essentially have three options to consider after a nodule is identified: (1) active surveillance; (2) additional diagnostic procedures, including positron emission tomography (PET), biopsy (percutaneous or bronchoscopic), and surgical removal; or (3) no further monitoring or workup (17, 18). Optimizing benefit and reducing risk for patients undergoing nodule evaluation requires the patient and clinician to balance a desire for the certainty of a diagnosis against the tolerance for the unknown, while assessing the likelihood of malignancy, the yield and risk of invasive procedures, and the potential risk of delayed diagnosis and treatment of cancer. Patients with pulmonary nodules want to know how likely the nodule is to be cancer, what are the safest and most reliable methods of diagnosis, which nodules can be serially observed and which need more invasive evaluation, and what are the best ways to discuss these concerns with their clinicians (19, 20). For the most part, answers to these fundamental questions are based on limited, indirect, or low-quality evidence.

We convened a workshop to establish a framework for lung nodule evaluation research and to facilitate the pace, impact, and efficiency of discovery. Outlining important research questions and potential strategies for evaluation by multidisciplinary groups can better and more effectively address the needs of patients (21).

### Methods

We assembled an international multidisciplinary (medical oncology, nursing, pulmonary, radiology, thoracic surgery, and public health) group of researchers, clinicians, and patient advocate stakeholders with expertise in pulmonary nodules at the May 2013 ATS International Conference. We obtained representation from the following ATS committees and assemblies: Documents Development and Implementation Committee, Patient and Family Education Committee, Behavioral Science and Health Services Research Assembly, Clinical Problems Assembly, Nursing Assembly, Thoracic Oncology Assembly, and the Patient Advisory Roundtable (COPD Foundation and Free to Breathe). Conflicts of interest were disclosed and managed according to the policies and procedures of the ATS.

The chairs (C.G.S. and M.K.G.) identified several topics for discussion that were vetted before the workshop. Participants were selected as moderators for breakout sessions, and each provided input about the planned agenda. We selected six focus areas: (1) diagnostic imaging and invasive procedures, (2) biomarkers, (3) prognostic models, (4) emerging treatments, (5) logistics and implementation, and (6) patient-centered outcomes.

The workshop consisted of presentations by experts in related fields, including screening for colorectal cancer, comparative effectiveness research, and lung cancer biomarker research. After these presentations, each participant engaged in breakout sessions in two of the focus areas, depending on interest. We did not use formal checklists or consensus methods, because we did not intend to prioritize one area or specific topic over another (21).

If available, participants considered the findings of systematic reviews when evaluating these topics but did not conduct new or updated reviews. Participants discussed key questions related to five topics: (1) identify the information/knowledge gaps, (2) identify why the topic is important, (3) identify relevant stakeholders, (4) review appropriate methods and approaches to address the gaps, and (5) identify potential sources of research funding.

Participants also suggested potential derivatives. For example, we identified tools or methods that would enhance or facilitate research efforts. Participants also identified potential products that could be developed after evaluating many of the key questions. Each item includes: (1) a description, (2) how it would improve care or advance the field, (3) what resources would be required for development, (4) what resources would be required for validation and evaluation, and (5) how would it be implemented.

After the workshop, a writing committee drafted a report based on an
Results

We identified several key questions and
derivatives (Tables 1 and 2) for each focus
area as well as several themes that
overlapped multiple areas. These cross-
cutting themes are discussed first, followed
by a section for each focus area.

Framing Research Questions for
Novel Diagnostic Procedures

There is a fair amount of evidence that novel
diagnostic imaging and invasive procedures,
biomarkers, and predictive models can
improve diagnostic accuracy and predict the
risk of future events, such as developing lung
cancer. Unfortunately, the evaluation of
most of these tests and algorithms has been
limited to uncontrolled studies of diagnostic
accuracy performed in specialized centers.
There are limited data regarding whether
they influence outcomes that are more
important to patients, clinicians, and/or
healthcare systems. We agreed that novel
diagnostic procedures should be proven to
provide incremental value above and beyond
currently available information before they
are widely adopted into clinical care.

Many novel diagnostic tests and
procedures have promise for improving care
for patients with pulmonary nodules. These
include imaging methodologies, such as
computer-aided detection (X-ray [22] and
CT scan [23–25]), computer-aided diagnosis
(CAD) [26–29], volume and mass analysis
[30, 31], gated PET imaging (32, 33), PET
imaging using novel radioactive tracers (32,
33), novel algorithms to reconstruct CT
images allowing lower radiation dose
(32–34) (e.g., model-based iterative
reconstruction), and procedures such as
navigational bronchoscopy and radial
ultrasound (17). There is also great potential
for novel biomarkers to distinguish benign
from malignant nodules and aggressive
versus relatively indolent cancers (35, 36).
Biomarkers can be classified in multiple
ways based on anatomic site of sampling
(e.g., serum, sputum, urine, and exhaled
breath markers), target of detection (e.g.,
DNA methylation, gene expression, and
ELISA), or type (e.g., DNA, microRNA, and
autoantibody). In addition, several models
using patient and nodule characteristics for
predicting cancer risk in patients with solid
nodules have been developed (37–41), but
more studies are needed to determine
whether these models provide incremental
value above and beyond clinical judgment
and intuition (42).

It is critical to develop novel diagnostic
tests and strategies to improve diagnostic
accuracy for patients with pulmonary
nodules. But at least over the short term, it
might be more impactful to demonstrate that
existing diagnostic technologies improve
patient-centered outcomes. Use of defined
phases of research should guide how these
tests are evaluated (43–46) (Figure 1). Few to
no prospective trials of diagnosis or the
impact of potential novel tests or strategies
on clinical outcomes have been performed.

It is important to consider which tests
show the most promise to impact clinical
practice when choosing candidates for
prospective studies. Currently, most patients
with nodules undergo follow-up CT scans
(16). Given the relatively low risk of serial
imaging, the negative predictive value of
a novel test will likely need to be very high to
substantially reduce the number of patients
who require follow-up imaging or the total
number of scans these patients receive.
 Conversely, a novel test would need to have
very high positive predictive value to
recommend surgical resection when
information from currently available imaging
studies suggests the nodule is benign or can
be safely monitored. Accordingly, studies
that report the likelihood of how the
biomarker would change decision-making
(e.g., the net reclassification index [47]) may
be useful to guide decisions for which tests
should be studied past Phase 2 (Figure 1). In
addition, explicit information of the risks of
the novel test (including invasiveness and
costs to patients and systems), feasibility, and
data regarding the potential use of the test
(see Reference 48 as an example) would
strengthen research proposals.

Although developed for biomarkers, use
of the prospective-specimen-collection and
retrospective-blinded-evaluation (PRoBE)
design may improve the rigor of intermediate
phases of novel test development and could
strengthen research proposals for other
diagnostic tests and strategies (45). The crux
of the PRoBE design requires a priori
consideration of how the novel test will
change diagnostic accuracy above current
methods while also stipulating data
collection processes. Furthermore, while
awaiting trials for evidence regarding the
impact of diagnostic imaging and
procedures on health outcomes, it may be
helpful to use evidence-based grading
systems to more formally evaluate their
clinical utility (49, 50).

Nodule Registries

The pace of discovery would be substantially
improved through the creation of nodule
registries. Current research is stymied by the
lack of reliable methods to identify patients
with nodules in routine practice. Notably, the
ATS and American College of Chest
Physicians recommend the use of a registry to
support lung cancer screening efforts, and use
of a registry is required by the Centers for
Medicare and Medicaid Services (51, 52).
Registries should be based on protocolized
radiology reports, with detailed information
regarding imaging and nodule characteristics
and recommendations (53). As an example,
the Lung Imaging Reporting and Data
System (Lung-RADS), developed by the
American College of Radiology to support
lung cancer screening, is a reporting tool (54,
55) that could serve as one element of
a registry. Ideally, data regarding risks for
lung cancer and nodule development, such
as age, smoking characteristics, occupational
exposures (e.g., asbestos), family history, and
geographic information (e.g., residence in
endemic fungal areas and radon exposure)
would be linked with the electronic medical
record. Natural language processing is
increasingly used to identify nodule
characteristics and may be useful to identify
other data from the electronic medical
record that are not routinely collected in
individual data fields (56).

Registries should incorporate data
regarding oncologic outcomes, procedures
Table 1. Summary of Key Questions

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Importance</th>
<th>Stakeholders</th>
<th>Methods/Approaches</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Diagnostic imaging and invasive procedures</td>
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<tr>
<td>Question 1: How can we validate current practice guidelines for the evaluation of lung nodules?</td>
<td>Determine the proper balance of benefit and harm at the patient and system level</td>
<td>Patients (P, R, TS)</td>
<td>Comparative effectiveness research methodologies</td>
<td>AHRQ</td>
</tr>
<tr>
<td>Effectiveness of and adherence to the current practice guidelines, associated patient outcomes, and resource use engendered by the guidelines are unknown, especially for subsolid nodules</td>
<td>Determine the cost effectiveness of evaluation strategies</td>
<td>Industry</td>
<td>Cost-effectiveness methods</td>
<td>ACRIN</td>
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<tr>
<td></td>
<td>Determine clinician adherence based on guidelines</td>
<td>Payers</td>
<td>Randomized and pragmatic trials of evaluation strategies</td>
<td>Foundations</td>
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<tr>
<td></td>
<td>Determine when to incorporate into clinical practice</td>
<td>Guideline developers</td>
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<td>NIH (NHLBI/NCI)</td>
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<td></td>
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<td>VA</td>
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<tr>
<td>Question 2: How and when should advances in image-based detection and characterization of lung nodules (e.g., computer-aided detection methods) and nonsurgical biopsy techniques become incorporated into clinical practice?</td>
<td>Identification and reporting of lung nodules is unpredictable</td>
<td>Patients</td>
<td>Comparative effectiveness research methodologies</td>
<td>AHRQ</td>
</tr>
<tr>
<td>Ability to measure and characterize nodules is inconsistent</td>
<td>Ability to measure and characterize nodules is unpredictable</td>
<td>Clinicians (P, R)</td>
<td>Comparing effectiveness of test characteristics in usual care settings and risks/benefits of use</td>
<td>Industry</td>
</tr>
<tr>
<td>Surveillance practices vary</td>
<td>Surveillance practices vary</td>
<td>Healthcare systems</td>
<td>Cost-effectiveness methods</td>
<td>NIH (NHLBI/NCI)</td>
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<tr>
<td>No definition of the added value of a new technology</td>
<td>No definition of the added value of a new technology</td>
<td>Industry</td>
<td>Randomized and pragmatic trials of new technologies</td>
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<td>Quasi-experimental approaches</td>
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<td>Biomarkers</td>
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<tr>
<td>Question 1: Can we optimize biomarker acquisition from small specimens?</td>
<td>Acquisition of adequate tissue for assessment of potential biomarkers</td>
<td>Patients (MO, P, TS)</td>
<td>Bench research to determine feasibility</td>
<td>AHRQ</td>
</tr>
<tr>
<td>Amount of histological and molecular information required from small specimens is increasing</td>
<td>Prioritization of testing as number of targeted therapeutics increase</td>
<td>Healthcare systems</td>
<td>Comparative effectiveness methodologies, including evaluation of proposed procedures</td>
<td>Cooperative oncology groups</td>
</tr>
<tr>
<td>Optimal procedures to provide sufficient specimens are unknown</td>
<td>More accurate prediction of rates of growth and risk of malignancy</td>
<td>Industry</td>
<td>Observational studies</td>
<td>SWOG</td>
</tr>
<tr>
<td>Quality of procedures in clinical settings is unknown</td>
<td></td>
<td>Payers</td>
<td>Translational research to determine efficacy of biomarker acquisition in a usual care setting</td>
<td>DOD</td>
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<td>Policy makers</td>
<td>Randomized and pragmatic trials of new technologies</td>
<td>Foundations</td>
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### Table 1. (Continued)

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<th>Gaps</th>
<th>Importance</th>
<th>Stakeholders</th>
<th>Methods/Approaches</th>
<th>Funding</th>
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<tbody>
<tr>
<td>Question 2: Can risk biomarkers distinguish between benign and malignant pulmonary nodules as well as aggressive and nonaggressive tumors?</td>
<td>Pathogenesis of cancer development, growth, and spread is poorly understood</td>
<td>Patients</td>
<td>Bench development of biomarkers</td>
<td>ATS</td>
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<td></td>
<td>Current clinical prediction models may not be sufficiently accurate to influence practice</td>
<td>Clinicians (P, RO, TS)</td>
<td>Validation studies</td>
<td>DOD</td>
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<td></td>
<td>Use of biomarkers may improve discrimination between benign and malignant nodules</td>
<td>Healthcare systems</td>
<td>Comparative effectiveness research methodologies</td>
<td>EDRN</td>
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<td></td>
<td>Benefit of new technologies should outweigh harms and costs both at patient and population level</td>
<td>Industry</td>
<td>Randomized and pragmatic trials, including examination of observation surveillance vs. biopsy, guided by biomarker risk assessment</td>
<td>Industry</td>
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<td>Policy makers</td>
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<td>NIH (NCI)</td>
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<td>Prognostic models</td>
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<tr>
<td>Question 1: What clinical, laboratory, and radiologic characteristics can be used to improve lung cancer risk prediction and improve subsequent outcomes?</td>
<td>Models for estimating the probability of malignancy in patients with solid solitary pulmonary nodules have been developed and validated at population level but not in routine practice settings</td>
<td>Patients</td>
<td>Comparative effectiveness research methodologies, including evaluation of risk factors, radiologic features, and novel biomarkers</td>
<td>Foundations</td>
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<td></td>
<td>Widespread adoption of lung cancer screening will increase the number of smokers identified with subsolid and/or multiple nodules</td>
<td>Clinicians (P, R, TS)</td>
<td>Validation across multiple settings and populations</td>
<td>NIH (NCI)</td>
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<td>Accurate assessment of the risk of lung cancer has important implications for the need of additional, and potentially invasive, follow-up procedures</td>
<td>Healthcare systems</td>
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<td>Medical societies</td>
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<tr>
<td>Question 2: Which small, slow-growing nodules can be observed with serial imaging vs. requiring biopsy or resection?</td>
<td>Risk of invasion and/or metastasis for slow-growing, potentially malignant lung nodules is not well characterized</td>
<td>Patients</td>
<td>Observational studies evaluating the association of risk factors, radiologic features, and novel biomarkers with risk of aggressive, invasive cancer</td>
<td>DOD</td>
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<td></td>
<td>Which subset of slow-growing 1- to 3-cm nodules can be followed with serial imaging vs. need for biopsy and/or treatment is unclear</td>
<td>Clinicians</td>
<td>Validation across multiple settings and populations</td>
<td>Foundations</td>
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<td>Healthcare systems</td>
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<td>Medical societies</td>
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<td>Emerging treatments</td>
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<tr>
<td>Question 1: What is the effectiveness of SBRT and other ablative therapies for patients with stage IA NSCLC?</td>
<td>Despite increases in the use of SBRT for stage IA NSCLC, its effectiveness compared with surgical resection for operable patients has not been established</td>
<td>Patients</td>
<td>Comparative effectiveness research, including resection vs. SBRT</td>
<td>Cooperative oncology groups</td>
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<td></td>
<td>Many patients with nodules are not candidates for anatomic surgical resection</td>
<td>Clinicians (P, RO, TS)</td>
<td>Trials (SBRT ongoing trials have encountered difficult recruitment)</td>
<td>NIH (NCI)</td>
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<td>Emerging therapies for early-stage NSCLC will influence upstream diagnostic testing and decision-making, including the necessity of definitive tissue diagnosis</td>
<td>Healthcare systems</td>
<td>Cost-effectiveness methods</td>
<td>VA</td>
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<td></td>
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<td>Industry</td>
<td>Multicenter phase II trials to evaluate ablative procedures such as RFA, cryoablation, and microwave ablation</td>
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<td>Payers</td>
<td>Randomized phase II trial to compare RFA to SBRT for stage IA NSCLC</td>
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<td>Policy makers</td>
<td>with tumors ≤ 3 cm</td>
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<td>Gaps</td>
<td>Importance</td>
<td>Stakeholders</td>
<td>Methods/Approaches</td>
<td>Funding</td>
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<td>Question 2: What interventions or therapies may stop or slow the growth rate of lung cancer that is identified as small nodules?</td>
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<td>Low-quality evidence suggests some therapies may prevent the development of cancer in high-risk patients</td>
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<td>Evidence for the effectiveness of treating patients with nodules with these potential therapies is lacking</td>
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<td>Chemoprevention has strong potential to improve mortality and reduce morbidity</td>
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<td>Any potential treatment needs to be very safe and well tolerated because many patients with nodules do not have lung cancer</td>
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<td>Patients</td>
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<td>Policy makers</td>
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<td>Comparative effectiveness research, including analysis of administrative data</td>
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<td>Multicenter phase II trials</td>
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<td>Randomized trials</td>
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<td>Cooperative oncology groups</td>
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<td>NIH (NCI)</td>
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Implementation

Question 1: How should nodule evaluation processes and tools be implemented to optimize risks and benefits?

Which nodule evaluation strategies can be implemented in routine-care settings that maximize patient-centered outcomes is unclear

Limited evidence suggests systemic, standardized, and multidisciplinary approaches to nodule evaluation are associated with better outcomes

Unclear which processes and strategies offer the most benefit to patients with least risk and appropriate resource use

Patients |
| Clinicians (N, MO, P, R, RO, TS) |
| Healthcare systems |
| Payers |
| Policy makers |
| Medical societies |
| Comparative effectiveness methodologies |
| Randomized and pragmatic trials |
| Foundations |
| Healthcare systems |
| NIH (NCI) |
| VA |

Question 2: Which, if any, performance measures and quality metrics should be incorporated into routine practice?

Which, if any, performance measures will most positively impact practice is unclear

Current guidelines are based on low-quality evidence, and inappropriate use of performance measures may negatively impact outcomes

Quality assessment is essential for developing high-quality care and minimizing harms

Patients |
| Clinicians (N, MO, P, R, RO, TS) |
| Healthcare systems |
| Payers |
| Policy makers |
| Medical societies |
| Comparative effectiveness methodologies |
| Randomized and pragmatic trials |
| Foundations |
| Healthcare systems |
| NIH (NCI) |
| VA |

Patient-centered outcomes

Question 1: What are the unmet needs and critical concerns of patients, families, clinicians, and other stakeholders surrounding pulmonary nodule evaluation?

Clinicians, researchers, and other stakeholders may not understand patients’ concerns

Relevant stakeholders have not discussed competing priorities and unmet needs of different parties

Patient needs should drive agenda for further research and improvements in patient care

All stakeholders should have a voice

Patients |
| Clinicians (N, MO, P, R, RO, TS) |
| Healthcare systems |
| Payers |
| Policy makers |
| Techniques to build consensus, give all stakeholders a voice, and prioritize topics (e.g., modified Delphi approach, nominal group technique, analytic hierarchy process) |
| Patient-centered outcomes research, including mixed qualitative and quantitative methods to elicit patient views |
| AHRQ |
| DOD |
| Foundations |
| NIH (NCI) |
| PCORI |
| VA |

(Continued)
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Importance</th>
<th>Stakeholders</th>
<th>Methods/Approaches</th>
<th>Funding</th>
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</thead>
<tbody>
<tr>
<td>Most patients do not understand their personal risk of lung cancer</td>
<td>Poor communication processes may lead to distress and anxiety</td>
<td>Patients</td>
<td>Patient-centered outcomes research, including observational, mixed qualitative</td>
<td>AHRQ</td>
</tr>
<tr>
<td>Patient–clinician communication is suboptimal in the context of lung</td>
<td>Overestimating lung cancer risk may lead to inappropriate choices (e.g., resection of low-risk nodule, longer than necessary follow-up)</td>
<td>Clinicians (N, MO, P, R, RO, TS)</td>
<td>and quantitative methods to evaluate the association of risk communication with</td>
<td>DOD</td>
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<tr>
<td>nodule evaluation</td>
<td>Underestimating lung cancer risk may be associated with harmful behaviors (continued smoking) and nonadherence with nodule evaluation</td>
<td>Healthcare systems</td>
<td>patient-centered outcomes</td>
<td>Foundations</td>
</tr>
<tr>
<td>Most patients and clinicians do not optimally engage in shared</td>
<td>Suboptimal decision-making processes in which patient views are not fully incorporated may be associated with patient distress and nonadherence with subsequent screening or nodule evaluation</td>
<td>Payers</td>
<td>Randomized and pragmatic trials of communication and/or decision-making tools</td>
<td>NIH (NCI)</td>
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<td>decision-making, including in setting of nodule evaluation</td>
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<td>Policy makers</td>
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**Definition of abbreviations:**
- ACR = American College of Radiology
- ACRIN = American College of Radiology Imaging Network
- AHRQ = Agency for Health Care Research and Quality
- ATS = American Thoracic Society
- DOD = Department of Defense
- EDRN = Early Detection Research Network
- MO = medical oncology
- N = nursing
- NCI = National Cancer Institute
- NIH = National Institutes of Health
- NSCLC = non–small cell lung cancer
- P = pulmonary
- PCORI = Patient-Centered Outcomes Research Institute
- R = radiology
- RFA = radiofrequency ablation
- RO = radiation oncology
- SBRT = stereotactic body radiotherapy
- TS = thoracic surgery
- VA = Department of Veterans Affairs
<table>
<thead>
<tr>
<th>Description</th>
<th>How/Why?</th>
<th>Development Resources</th>
<th>Validation/Evaluation</th>
<th>How/Where?</th>
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<tbody>
<tr>
<td><strong>Cross-cutting derivatives</strong></td>
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<tr>
<td>Nodule registries: EMR-based radiology reports with links to patient-level administrative data for identification and description of lung nodules on chest imaging</td>
<td>Development of clinically useful EMR-based registries, potentially aided by natural language processing, will facilitate ongoing research and quality improvement initiatives Identifying patients with nodules and associated clinical and radiological characteristics is currently very expensive or impractical Could reduce variability in practice Could inform clinicians about appropriate management</td>
<td>ATS (BSHSR, Clinical Problems, nursing, TOA) Other professional societies Consensus statement on reporting elements, incorporation into reporting systems/EMR</td>
<td>Multicenter adoption and tracking of subsequent management Compare to prior management</td>
<td>Make available on ATS (and other) websites once validated Cooperate with providers of reporting systems or EMR to incorporate Partner with other stakeholders such as the American College of Radiology, ACCP, Society of Thoracic Surgeons, American Society for Radiation Oncology, American College of Physicians</td>
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<tr>
<td>Consortiums to pool clinical data and specimens for biomarker development and validation in screening centers</td>
<td>Could provide diverse, unbiased approach to validate biomarkers and strategies to implement biomarkers Could guide use of biomarkers, refine diagnostic approach to lung nodules</td>
<td>ATS (TOA, RCMB, Clinical Problems) Grants: NCI Healthcare systems Payers Policy makers</td>
<td>Patient testing Lab testing Clinician testing</td>
<td>Potential partners include ATS, DOD/VA, foundations, IASLC, NCI and CRN, NIH-NHLBI</td>
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<tr>
<td>Development of a framework and consensus manual on added value of new technologies for the evaluation of pulmonary nodules</td>
<td>Could provide minimal requirements or gold standards for the level of evidence of the study itself, mathematical evaluation of added value, balance of gain in diagnostic accuracy vs. additional efforts and costs of the new technology. Could improve translation of research outcomes to clinical practice and to educate clinicians</td>
<td>Consensus statement developed by working group connected to association (researchers, clinicians, patients, systems, payers, grant funders)</td>
<td>Multicenter adoption and tracking of subsequent management Pragmatic trials Comparative effectiveness research methodologies</td>
<td>Connect to ATS/ACCP to form working group of interested experts Review of literature and consensus meetings</td>
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<td><strong>Diagnostic imaging and invasive procedures</strong></td>
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<td>Evidence-based, easily electronically accessed (web, mobile applications) user (clinician and patient)-friendly lung cancer risk stratification tools for pulmonary nodules. Could include unbiased information on lung cancer risk stratification, commercially available diagnostic tests, and listings of clinical expertise based on availability of technologies and nodule clinics</td>
<td>Could improve risk estimation by clinicians. Could provide tailored information for patients. Could improve information dissemination, regionalization, decision-making, and resource use</td>
<td>ATS (BSHSR, Clinical Problems, nursing, TOA) Other professional societies Healthcare systems Payers Policy makers</td>
<td>Patient testing Lab testing Clinician testing Feedback section on website</td>
<td>Conference Peer-reviewed journal Research study ATS website Website developer, content development, connection to an association (e.g., ATS, ACCP, patient advocacy group)</td>
</tr>
<tr>
<td>Description</td>
<td>How/Why?</td>
<td>Development Resources</td>
<td>Validation/Evaluation</td>
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<tr>
<td>Biomarkers</td>
<td>Could provide education to interventional pulmonary programs. Could enhance standardization of protocols and innovation to improve performance</td>
<td>ATS/ACCP</td>
<td>Patient testing</td>
<td>Conference</td>
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<td>Grants</td>
<td>Lab testing</td>
<td>Peer-reviewed journal</td>
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<td>Healthcare systems</td>
<td>Clinician testing</td>
<td>Research study</td>
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<td>Implementation</td>
<td>Could improve quality and adherence to guidelines. Could facilitate reporting of nodule and patient characteristics</td>
<td>Healthcare systems</td>
<td>Stakeholder consensus</td>
<td>Output from stakeholder conference</td>
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<td>Patient stakeholder groups</td>
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<td>Policy makers</td>
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<td>Professional societies</td>
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<tr>
<td>Patient-centered outcomes</td>
<td>Uses formal methods to obtain consensus from multiple stakeholders. Sets a research agenda based on needs identified as most important to patients, with input from multiple stakeholders</td>
<td>ATS (BSHSR, Clinical Problems, nursing, TOA, PAR)</td>
<td>Elicit feedback from others not involved in group but pulled from same stakeholder groups to ensure face validity</td>
<td>Conference</td>
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<td>Healthcare systems</td>
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<td>Other professional societies</td>
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<td>Patients</td>
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<td>Patient advocacy organizations</td>
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<td>Professional societies</td>
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<td>Instruments that measure decision quality specific to issues surrounding lung cancer screening and nodule evaluation</td>
<td>Context-specific instruments better able to measure decision quality than generic instruments. Could help measure effect of decision support tools</td>
<td>ATS (BSHSR, Clinical Problems, nursing, TOA)</td>
<td>Patient testing</td>
<td>Conference</td>
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<td>Individually tailored patient- and clinician-accessible communication aids, including decision support tools and educational materials that address key patient questions and improve satisfaction with decision-making</td>
<td>Could improve patient-clinician communication processes. Could allow patients to weigh options based on their own preferences and values. Could facilitate shared decision-making</td>
<td>ATS (BSHSR, Clinical Problems, SOTO, PAR)</td>
<td>Patient testing</td>
<td>Conference</td>
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</table>

**Definition of abbreviations:** ACCP = American College of Chest Physicians; ATS = American Thoracic Society; BSHSR = Behavioral Science and Health Services Research; CRN = Cancer Research Network; DOD = Department of Defense; EMR = electronic medical record; IASLC = International Association for the Study of Lung Cancer; NCI = National Cancer Institute; NIH = National Institutes of Health; PAR = Public Advisory Roundtable; PCORI = Patient-Centered Outcomes Research Institute; RCMB = Respiratory Cell and Molecular Biology; SOTO = Section on Thoracic Oncology; TOA = Thoracic Oncology Assembly; VA = Veterans Affairs.
(including complications), smoking cessation efforts, adherence to management guidelines, and resource use. The Surveillance, Epidemiology, and End Results (SEER)–Medicare Program (57) collects similar information and should guide the collection of patient-level variables. Healthcare systems may want to emulate the registry used by the Department of Veterans Affairs to support its pilot lung cancer screening program (58). Some data may be challenging to collect by individual systems because patients frequently receive care at multiple institutions, so processes will need to be developed to link nodule data via healthcare information exchange.

Registries should ideally be a core component of system-level interventions to facilitate patient care. They are unlikely to gain traction if solely used for research purposes. They should optimize current practices and information technology systems to be feasible, user friendly, and cost effective. Registries could be used to track patients to improve adherence to follow-up plans and longitudinally follow changes in nodule characteristics. Given that most institutions lack systematic methods to identify or follow patients with nodules, registries could guide quality-improvement efforts. They could also be used as recruitment tools for trials and in comparative effectiveness research (59). Finally, registries themselves should be evaluated for their impact on patient-centered outcomes, healthcare system resource use, and costs.

**Data Sharing**

Registries are necessary but not sufficient to improve research efforts. Methods to share the data in registries are also required. For example, nodule consortiums could facilitate validation of prognostic models and increase the ability to test their clinical effectiveness. In addition, consortiums to pool clinical data with specimens should be developed. The ability to compare different diagnostic tests and implementation strategies will also be greatly facilitated by consortiums.

In particular, biomarker studies are often limited by lack of generalizability and inability to validate the marker in other settings. Registries should collect data regarding small sample acquisition and processing and have the ability to be linked with specimen banks. Several existing groups and consortiums could serve as models for collaboration, including COPD Outcomes-based Network for Clinical Effectiveness and Research Translation (CONCERT), the Early Detection Research Network of the National Cancer Institute, and the American College of Chest Physicians Quality Improvement Registry (AQuIRE) (60) (61–63).

**Diagnostic Imaging and Invasive Procedures**

Practice guidelines for the evaluation of lung nodules must be studied. Current recommendations regarding follow-up imaging and procedures after nodule detection (15–17) are based on indirect evidence regarding the risk of malignancy, the expected growth rate of malignant nodules, the capability to detect growth, and the risks of radiation, rather than evidence from randomized trials or large, well-designed observational studies.

Guidelines for the management of subsolid nodules are grounded in even weaker evidence than those for solid nodules and should also be studied (15). It may also be helpful for guideline developers to use a living guideline model to more rapidly and efficiently disseminate important developments in the field (64).

**Biomarkers**

Given expected changes in treatment options, it will be important to obtain adequate samples from small specimens. Although most developmental work to date has used specimens from patients with advanced lung cancer, more research is required to understand the accuracy and prognostic value of biomarkers in local and regional stage disease. Optimizing the ability to test for multiple markers in small samples will also help to evaluate pathogenesis of cancer development, growth, and spread. Focusing biomarker studies on mechanistic factors will facilitate development of targeted therapies that can decrease or stop malignant nodule growth and metastasis.

**Prediction and Prognostic Models**

It is important to determine what factors accurately estimate the probability of lung cancer among patients with nodules and whether their use leads to improved outcomes. Several models for predicting cancer risk in patients with solid nodules have been developed, but they require additional validation (37–41). Only one model has explicitly included identification of multiple nodules as a predictor (39). No model has been developed for subsolid nodules, a common finding among subjects undergoing lung cancer screening. It is also important to assess the value of incorporating into future models readily available CT scan findings, such as the presence of emphysema. Another key issue is related to the concern for overdiagnosis of screening-detected nodules. Models that accurately predict nodule growth, invasion, and metastasis or other determinants of prognosis would be valuable to clinicians and patients and may help reduce overtreatment of slow-growing cancers. Finally, it will be
useful to follow the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) reporting guidelines (65, 66).

**Emerging Treatments**

Treatment options for early-stage lung cancer directly impact the evaluation of pulmonary nodules (17, 18) and thus should be rigorously evaluated. For instance, stereotactic body radiotherapy (SBRT) has rapidly disseminated as a treatment for patients with stage I non-small cell lung cancer at high risk for perioperative morbidity and mortality. A variety of other ablative therapies, such as radiofrequency ablation (RFA), cryoablation, and microwave ablation, have been used for inoperable patients (67). However, there are no randomized trials comparing ablative therapies to surgery (67), and recent studies of SBRT versus sublobar resection were terminated early due to poor accrual (68). Because of the risks and challenges of biopsy in marginal surgical candidates, many patients with nodules undergo ablative therapy without a diagnosis of lung cancer (69). It will be important to compare the efficacy and effectiveness of emerging therapies to surgery to guide decision-making about the risks and benefits of different evaluation strategies and treating patients with pulmonary nodules that may not be cancerous. Guidelines (17) and decision models (70) should be evaluated for which patients SBRT constitutes acceptable treatment when a tissue diagnosis is not established.

It is also important to study the effectiveness of novel therapies on cancer prevention and tumor growth among patients with nodules. Trials of novel prevention agents and comparative effectiveness studies of potential existing therapies (e.g., oral or inhaled iloprost) should be conducted (71). Nodule growth on surveillance imaging may be an important intermediate outcome in these trials if they are underpowered to detect differences in lung cancer mortality (72).

**Logistics and Implementation**

Processes for nodule evaluation should be optimally implemented into routine care settings, because many patients do not receive guideline-adherent follow up (73, 74). Evidence supporting specific system-level interventions for nodule evaluation is limited, but these have been shown to be helpful in other settings (75–77). Possible interventions could include: creation of multidisciplinary teams, standardized reporting of results, development of care pathways, and development of registries to track patients with nodules. It is important to study the facilitators and barriers, effects on health outcomes, unintended consequences, and cost effectiveness of these interventions.

Performance measures and quality metrics will undoubtedly be developed. Indeed, the dissemination of lung cancer screening into practice has been accompanied by calls to institute these measures (51, 78). However, there is little high-quality evidence on which to base specific measures or to establish quality thresholds. A multi-stakeholder group should identify potential metrics, categorize the evidence base for their use, and suggest steps for adoption and implementation. Possible quality indicators include accuracy of image acquisition and processing, timeliness of reporting, the use of a tracking system, the percentage of benign diagnoses among surgically resected nodules, the percentage of nondiagnostic bronchoscopy and CT-guided nodule biopsies, timely diagnosis and treatment of malignant nodules, and complication rates from biopsies and resections. The ATS has previously recommended that measures be subjected to rigorous review and testing before widespread implementation (79). In addition, it will be important to study the implementation process itself to more effectively and efficiently establish the interventions in real-world settings.

**Patient-centered Outcomes**

Patient centeredness is defined by the Institute of Medicine as care “that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions” (80). To conduct innovative patient-centered research, the field should incorporate feedback from diverse stakeholders to understand the unmet needs of patients, their families, and their clinicians. Some patients suffer psychological harm when a pulmonary nodule is discovered during screening (81–85) or incidentally (19, 20, 86, 87). We identified communication processes as the most likely factors that that could be modified to improve patient-centered outcomes. Tools and systems designed to improve communication processes should be evaluated regarding their effect on outcomes important to patients. To ensure these tools are helpful and ultimately used in practice, they should be developed with systematic input from stakeholders.

As a next step to this statement, it would be optimal to form an organized, multi-stakeholder group, similar to the CONCERT effort (88). Like CONCERT, this effort should use formal consensus processes to elicit concerns and unmet needs from multiple stakeholders. The purpose of the group would be to prioritize research and assess the evolving needs of the patient and research community.

**Discussion**

Our workshop identified many research questions regarding the evaluation of pulmonary nodules. Given the large numbers of patients affected, which is likely to increase with the implementation of lung cancer screening, it is critical to conduct research to answer the most pressing questions.

We developed the following key recommendations:

- The efficacy and effectiveness of new diagnostic strategies (including novel imaging tests and biopsy techniques, biomarkers, and prognostic models) should be evaluated using established phases of test development, from identification of a novel strategy or characteristic to establishment of clinical utility.
- Registries that link demographic and nodule characteristics with patient-level outcomes should be developed.
- Pulmonary nodule evaluation strategies are guided by subsequent treatment options for early-stage lung cancer, and these treatments should be rigorously studied.
- Potential interventions and quality metrics to improve nodule evaluation processes should be studied before requiring their implementation.
- Tests and interventions should be evaluated for their impact on patient-centered outcomes.

There were substantial overlaps in the key research gaps we identified. For instance, participants recognized the need to validate novel prediction models, imaging tests, invasive procedures, and biomarkers. We also agreed that these interventions need to be rigorously evaluated in randomized and/or pragmatic trials for their effects on patient, clinician, and healthcare system outcomes before widespread
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Conclusions
This statement establishes a research framework to address fundamental questions about the care of patients with pulmonary nodules. We engaged clinical and patient stakeholders to address questions of importance. This statement may help researchers develop impactful and innovative proposals and enable funders to better judge novel research proposals. We hope that it will quicken the pace and increase the efficiency of discovery to improve the quality of care for patients with pulmonary nodules.

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References


51. American Thoracic Society Documents


