

Systems-Level Resources for Pulmonary Nodule Evaluation in the United States: A National Survey

To the Editor:

Each year, more than 1.5 million Americans are found to have a pulmonary nodule (1). As lung cancer screening becomes prevalent, still more nodules will be identified. Whether detected incidentally or through screening, guidelines recommend evaluating pulmonary nodules in a timely fashion to identify the subset that are malignant. Yet patients with pulmonary nodules often do not receive appropriate evaluation, seemingly “falling through the cracks” (2, 3). Systems-level structures and processes of care have been proposed to facilitate appropriate, efficient nodule evaluation (4–8), and indeed, clinicians have indicated that such system-level resources are essential to avoid loss to follow-up (9). However, the degree to which these structures and processes of care have been implemented nationally is unclear, and the American Thoracic Society (ATS) has called for more research in this area (10). We conducted a survey of ATS clinicians to characterize the availability of system-level resources to facilitate pulmonary nodule evaluation in the United States.

Methods

We surveyed clinician members of the ATS Respiratory Cell and Molecular Biology and Clinical Problems Assemblies (the parent assemblies of the Section of Thoracic Oncology at the time of survey administration). Eligible clinicians included physicians or midlevel providers who regularly saw patients in an outpatient clinic. ATS sent three e-mails in March and April 2014, inviting clinicians to participate in an anonymous online survey, with a \$50 incentive for completion. The 32-item survey asked about demographics, practice setting, and practices regarding lung cancer screening and nodule evaluation. The Boston University Institutional Review Board approved this study.

Although this was an international survey, we restricted analysis to responses from U.S. clinicians, given differences in resource availability and practice patterns across countries. Proportions were compared using chi-squared tests, and medians with the Kruskal-Wallis test, with two-sided $\alpha < 0.05$ as the threshold for statistical significance. All data were analyzed using Stata 10.1 (College Station, TX).

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Table 1. Respondent Characteristics

Characteristics	%
Male	74.3
Physician	99.1
Clinical specialty	
Pulmonary/critical care/sleep	90.5
Primary care/internal medicine	7.5
Cardiothoracic surgery	0.9
Radiology	0.6
Outpatient versus inpatient effort	
Exclusively outpatient	6.0
Mostly outpatient	49.2
Mostly inpatient	44.8
Practice type	
Academic	62.2
Community/health maintenance organization/other	30.0
Department of Veteran Affairs	7.8
Practice setting	
Urban	69.5
Suburban	24.8
Rural	5.7
Practice location	
Northeast	37.8
South	15.3
Midwest	27.8
West	19.1

Results

Of 5,872 ATS members with a valid e-mail address, 1,444 opened the survey invitation and 428 eligible clinicians participated (response rate, 7% overall; 30% of those who opened the e-mail). Table 1 shows the characteristics and practice settings of the 320 U.S. respondents.

The most common structures and processes of care in place were inclusion of Fleischner Society guidelines in radiology reports (82.7%), flagged prompts to the ordering provider on radiology reports with new nodules (59.4%), and staff members to facilitate nodule evaluation (e.g., scheduling appointments, 55.2%) (Figure 1). Most respondents reported some (median, 3; interquartile range, 2–5) system-level resources to facilitate nodule evaluation. Veterans Affairs (VA) sites tended to have more resources in place, with 88.0% reporting at least three (vs. 69.8% at academic centers and 53.1% at community/health maintenance organization facilities; $P < 0.001$). There was a broad distribution of reported resources within all groups, however, with 11 respondents (3.5%) reporting no structures or processes of care to facilitate nodule evaluation and eight respondents (2.5%) reporting nine or more system-level resources in place.

When comparing types of facilities, VA sites were significantly more likely to report electronic consults (64.0% VA, 15.7% academic, 7.4% community; $P < 0.01$; Figure 1). Clinicians in VA and academic settings were significantly more likely to report dedicated pulmonary nodule clinics than community/health maintenance organization physicians (48.0% VA, 49.5% academic, 10.6% community; $P < 0.01$). Academic settings were significantly more likely to report availability of same-day consults for pulmonary nodules (8.0% VA, 17.3% academic, 5.3% community; $P < 0.01$).

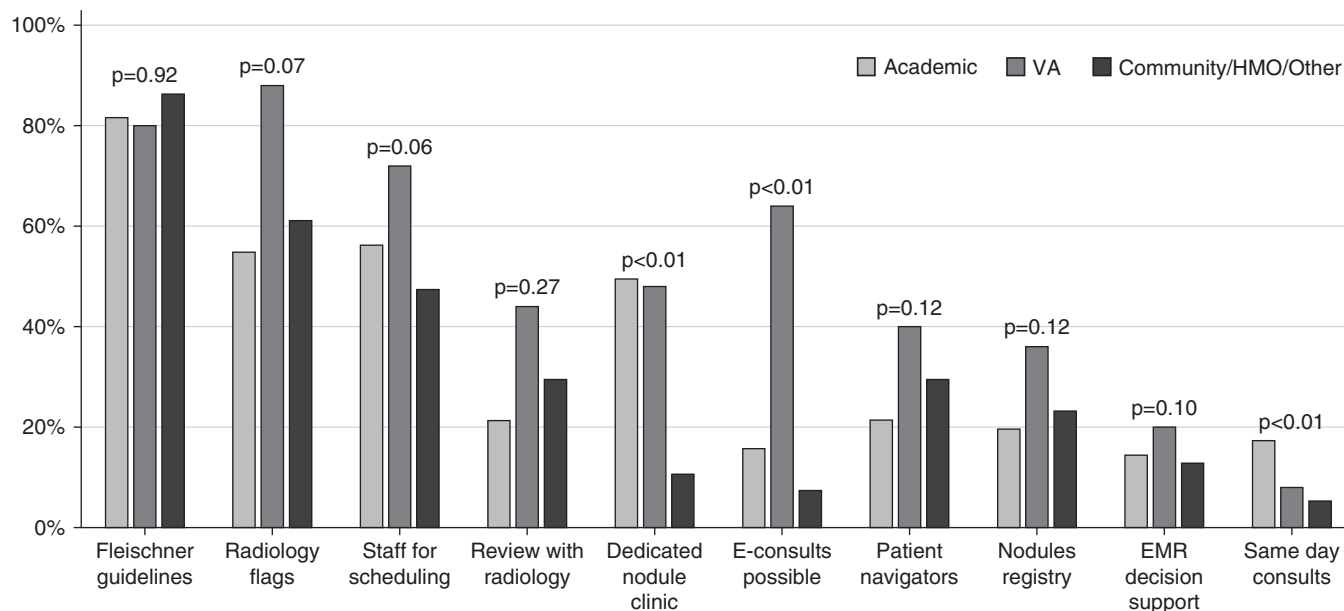


Figure 1. Systems-level resources in place to facilitate pulmonary nodule evaluation. E-consults = electronic consults; EMR = electronic medical record; HMO = health maintenance organization; VA = Veterans Affairs.

Discussion

This national survey identifies great variation in the availability of systems-level resources to facilitate pulmonary nodule evaluation across the United States. Although several structures and processes of care have been implemented to facilitate nodule evaluation, particularly in VA sites, only the use of templated reporting including guideline recommendations, radiology flags, and staff for scheduling have diffused to the majority of sites. Hence, at most sites, there is a missed opportunity to ensure patients with pulmonary nodules receive appropriate care. This raises questions about the preparedness of sites to implement comprehensive lung cancer screening programs, as professional societies recommend that screening programs have standardized structures and processes of care in place not only for screening but also for downstream evaluation and treatment of screen-detected nodules (7, 8).

This study has limitations. First, our response rate was relatively low. Moreover, respondents from urban academic centers were disproportionately represented, whereas VA clinicians represented a small minority of respondents. Thus, our results may not be broadly generalizable. Second, this survey was anonymous: We do not know what centers are represented and whether some sites may be represented by more than one respondent. Finally, our survey does not evaluate the actual resources in place or their quality.

The ATS has identified a need for research to establish which structures and processes most effectively improve outcomes of patients with pulmonary nodules so that facilities know how best to invest limited resources (10). As lung cancer screening is implemented, these studies are all the more urgently needed to assure appropriate resources are in place to facilitate pulmonary nodule evaluation. This study provides the first national data on availability of systems-level processes of care to facilitate pulmonary nodule evaluation, which is critical data to inform readiness for widespread implementation of lung cancer screening. ■

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Alpha-1 Antitrypsin Regulates Transcriptional Levels of Serine Proteases in Blood Mononuclear Cells

To the Editor:

PiZZ (Glu342Lys) alpha-1 antitrypsin deficiency (A1ATD) is a typical genetic risk factor associated with the development of early-onset chronic obstructive pulmonary disease (COPD) with emphysema. Because A1AT is a major circulating inhibitor of serine proteases (serpin), a severe deficiency of this protein may lead to lung tissue damage by uncontrolled activity of neutrophil elastase, proteinase 3 (PRTN3), and other serine proteases. In general, a proteinase/antiproteinase imbalance is among potential mechanisms implicated in the pathophysiology of COPD (1). The importance of A1AT in maintaining protease–antiprotease homeostasis is also supported by a positive correlation between a recently described *in vivo* marker of neutrophil elastase activity (A α -Val360) and disease severity in emphysema related to A1ATD (2). There is, however, considerable heterogeneity in the clinical expression among people with type ZZ A1ATD. Some

develop emphysema in early adulthood (35–45 years of age), whereas others in late adulthood or not at all, and severity of symptoms also varies.

Peripheral blood mononuclear cells (PBMCs) have emerged in recent years as surrogate markers of several diseases, including preeclampsia, rheumatoid arthritis, and malignant diseases (3, 4). COPD is also characterized by the altered features of PBMC. The dysfunction of PBMCs has been linked to acute exacerbations in COPD (5). We previously found that blood monocytes from patients with COPD released more matrix metalloproteinase-9 and IL-6 and showed nuclear factor- κ B activation compared with healthy controls (6). Current studies suggest that gene expression signatures in PBMCs could serve as markers of disease activity or expression in COPD (7).

We hypothesized that the PBMCs may have specific gene expression signatures that are related to clinically healthy PiZZ not present in PBMCs of PiMM (normal A1AT gene) carriers. To address this, we isolated cells from 8 PiZZ asymptomatic donors matched with 12 PiMM healthy donors (Table 1). Lung function tests and routine clinical laboratory analyses, including determination of serum A1AT concentration and genotype, were performed at the Department of Internal Medicine, Philipps-Universität Marburg, Germany. Every donor gave written informed consent for collection and use of blood samples for this study. The study was approved by the Marburg University ethics committee.

The PBMC were isolated using Lymphosep discontinuous gradient centrifugation, resuspended in RPMI 1640 (Gibco, Life Technologies, Waltham, MA) and incubated at 37°C and 5% CO₂. Afterward, PBMCs were used for mRNA preparation. Gene expression analysis by quantitative RT-PCR was assessed as described earlier, using two internal housekeeping genes: β -glucuronidase and β -actin (8). SPSS for Windows, release 21.0 (IBM, Armonk, NY) was used for the statistical calculations.

Our results indicate that adherent PiZZ PBMCs from asymptomatic donors express significantly higher levels of elastase (ELANE), PRTN3, and cathepsin G if compared with PBMCs from healthy PiMM donors (*see* Table 1). The relative expression of A1AT (SERPINA1) was slightly (by about 38%) lower in PiZZ than in PiMM PBMCs ($P < 0.05$). Moreover, relative expression of the SERPINA1 gene inversely correlates with expression of ELANE ($r = -0.82$; $P = 0.001$), PRTN3 ($r = -0.82$; $P = 0.001$) and cathepsin G ($r = -0.72$; $P = 0.006$) in PBMCs. This latter finding implies that A1AT probably regulates the expression of serine proteases. To provide additional support for this concept, we prepared mRNA from adherent PBMCs of 10 PiZZ patients with COPD who were receiving long-term infusion of plasma-purified A1AT protein (Prolastin, Grifols, Spain). Blood for PBMC isolation was taken just before patients received their next weekly infusion. Quantitative real-time polymerase chain reaction analysis was employed to assess the expression of ELANE, PRTN3, cathepsin G, and SERPINA1. All primers were obtained from Thermo Fisher Scientific (Waltham, MA). As shown in Table 1, PiZZ PBMCs from patients treated with Prolastin showed lower expression of all three enzymes relative to PiZZ PBMCs from healthy donors. Specifically, ELANE expression was lower by 50%. As expected, serum levels of A1AT were as follows: PiMM > PiZZ with Prolastin > PiZZ no Prolastin, and were inversely related to the expression levels of

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