same period. More targeted studies looking at factors associated with readmissions for COPD would shed additional light on the observed sex disparities.

Author disclosures are available with the text of this letter at www.atsjournals.org

Khushboo Goel, M.D.*
Morgan Bailey, M.D., M.P.H.
Mark Borgstrom, Ph.D.
Sairam Parthasarathy, M.D.
Bhupinder Natt, M.D.
Cristine Berry, M.D., M.H.S.
Christian Bime, M.D., M.Sc.
University of Arizona
Tucson, Arizona

ORCID ID: 0000-0002-3871-0513 (B.N.).

*Corresponding author (e-mail: khushboo.goel@ucdenver.edu).

References

1 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–2128.
2 Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010;65:480–485.
3 Watson L, Vestbo J, Postma DS, Decramer M, Rennard S, Kiri VA, *et al*. Gender differences in the management and experience of chronic obstructive pulmonary disease. *Respir Med* 2004;98:1207–1213.
4 Henoch I, Strang S, Löfdahl C-G, Ekberg-Jansson A. Management of COPD, equal treatment across age, gender, and social situation? A register study. *Int J Chron Obstruct Pulmon Dis* 2016;11:2681–2690.
5 Stein BD, Bautista A, Schumock GT, Lee TA, Charbeneau JT, Lauderdale DS, *et al*. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations. *Chest* 2012;141:87–93.
6 Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance–United States, 1971-2000. *MMWR Surveill Summ* 2002;51:1–16.
7 Doucet M, Rochette L, Hamel D. Incidence, prevalence, and mortality trends in chronic obstructive pulmonary disease over 2001 to 2011: a public health point of view of the burden. *Can Respir J* 2016;2016:7518287.
8 Molinari N, Briand C, Vachier I, Malafaye N, Aubas P, Georgescu V, *et al*. Hospitalizations for COPD exacerbations: trends and determinants of death. *COPD* 2015;12:621–627.
9 Rahmanian SD, Diaz PT, Wewers ME. Tobacco use and cessation among women: research and treatment-related issues. *J Womens Health (Larchmt)* 2011;20:349–357.
10 Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. *Eur Respir J* 2003;21:1017–1023.

Potential Delays in Diagnosis of Idiopathic Pulmonary Fibrosis in Medicare Beneficiaries

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease (ILD) of unknown cause, with median survival of 3 to 5 years (1). In 2014, two treatments that slow IPF progression gained U.S. Food and Drug Administration approval, highlighting the need for early, accurate diagnosis (2–4). Establishing a diagnosis of IPF can be challenging, with misdiagnoses and delays commonly reported (5–7). Despite evidence of diagnostic delays, developing a real-world estimate of this delay is difficult because of inclusion of data in IPF registries only after diagnosis, poor recall of symptom onset in surveys, and the disease's relative rarity (annual prevalence, 4.6–11.3/100,000) (8), preventing identification of adequate sample populations. Using Medicare claims data, which capture health service utilization for Americans 65 years and older, we examined patterns of diagnostic respiratory testing and pulmonologist visits that precede IPF diagnosis to investigate potential diagnostic delays. This research was previously presented at the American Thoracic Society 2017 conference, the 2017Aspen Lung Conference, and the CHEST 2017 meeting.

Methods

We analyzed claims data for all Medicare beneficiaries who were diagnosed with IPF in 2012. On the basis of a published algorithm for identifying beneficiaries with IPF in claims data (9, 10), beneficiaries were included if they: *1*) had one or more inpatient or two outpatient claims with IPF as a listed diagnosis in 2012 (3), *2*) had no claim with another ILD code (3) after the last observed IPF claim, *3*) had no claims with IPF within 5 years before the first qualifying IPF claim in 2012 (index date), and *4*) had one or more chest computerized tomography (CT) scans before index diagnosis.

Among included beneficiaries, we counted the following tests in the 5 years before IPF diagnosis: pulmonary function tests (PFTs), chest radiographs, chest CT scans, fiberoptic bronchoscopy, autoimmune serologies, 6-minute-walk test, cardiopulmonary exercise test, precipitin panels, arterial blood gas, oxygen saturation, and surgical lung biopsies. Time from first recorded test to diagnosis of IPF was measured and illustrated as cumulative probability curves. We reviewed claims for evaluation and management services to identify provider specialty; pulmonologist visits were reported similar to testing above. The study was exempted from institutional review board review.

Results

Among 33,780 Medicare beneficiaries with a qualified claims-based diagnosis of IPF in 2012, 7,306 met all criteria and formed the final sample. Beneficiary characteristics are summarized in Table 1. All beneficiaries had at least one diagnostic test of interest during the 5-year prediagnosis period, with the most common tests being chest radiographs (99.2%) and PFTs (75.0%) (the full list is provided in Table 2). Tests were associated with many provider specialties, often other than pulmonology. The time between tests and initial IPF diagnosis varied, although testing and pulmonologist visit frequency increased immediately before diagnosis (Figure 1).

The majority of beneficiaries ($n = 5,154$, 70.5%) had a pulmonologist visit within 5 years before IPF diagnosis (Table 2).

Genentech, Inc. provided financial support for this research.

Table 1. Patient demographics of patients newly diagnosed with idiopathic pulmonary fibrosis ($N = 7,306$)

Characteristic	Patients Newly Diagnosed with IPF
Age, yr	
Mean (standard deviation) [median]	80.8 (6.2) [81]
Minimum–maximum	70–105
Female	3,559 (48.7)
Race	
White	6,894 (94.4)
Black	212 (2.9)
Hispanic	56 (0.8)
Asian	40 (0.5)
Other/unknown	104 (1.4)
Region	
Midwest	1,880 (25.7)
Northeast	1,412 (19.3)
South	2,962 (40.5)
West/other/unknown	1,052 (14.4)

Definition of abbreviation: IPF = idiopathic pulmonary fibrosis.
Data presented as No. (%) unless otherwise noted.

Of these 5,154 beneficiaries, 34.7% had their initial pulmonologist visit more than 3 years before diagnosis.

The first chest CT scan was observed throughout the 5-year prediagnosis period, with 19.1% of beneficiaries having their first scan more than 4 years before IPF diagnosis, 32.5% more than 3 years before diagnosis, and 57.5% more than 1 year before diagnosis (Table 2). Repeated scans were common before index diagnosis.

Discussion

In a large, nationally representative sample of Medicare beneficiaries with IPF, chest imaging, PFTs, and pulmonologist visits were commonly performed in the 5 years before a diagnostic code for IPF appeared. Nearly one-third of beneficiaries had their first CT scan more than 3 years before diagnosis, with slightly more seeing a pulmonologist in this period. If these are proxies for development of IPF-related respiratory symptoms, our findings may mean that diagnosis of IPF is frequently delayed, even after evaluation by a pulmonologist.

Our results are consistent with previous studies (7). Lamas and colleagues (7) found a median delay of 2.2 years before an accurate diagnosis. Furthermore, diagnostic delay was associated with comorbidities such as coronary artery disease and gastroesophageal disease, to which symptoms of IPF may have been initially attributed. A survey study of patients with IPF reported more than half of patients were initially misdiagnosed, and 43% recalled a delay of 1 year or more from symptoms to diagnosis (6). Our study supports these findings by suggesting that diagnostic imaging and PFT are ordered often years before initial diagnosis, and that delayed diagnosis may potentially occur even after diagnostic tests and pulmonologist evaluation. This may point to a need to improve IPF diagnostic tests, testing algorithms, and/or test interpretation, even among pulmonologists. In addition, 30% of patients did not see a pulmonologist before diagnosis, possibly indicating the need for better access to subspecialty care. Improvement in chest CT scan capabilities and interpretation and early referral to an ILD center may reduce potential delays and expedite appropriate treatment.

Our study is limited, in that even with use of chest CT scans (not specific to high-resolution scans) and other respiratory testing, earlier diagnosis of IPF may not have been possible. The test results may have been unavailable, initially normal, or insufficient to diagnose IPF; beneficiaries may have initially lacked a radiographic usual interstitial pneumonia (UIP) pattern recommended for definite diagnosis or had testing that preceded the development of IPF diagnostic criteria on the basis of confidence of radiographic UIP pattern (11). In addition, surgical lung biopsy, itself a risk among elderly

Table 2. Frequency distributions of first diagnostic test and first pulmonologist visit in 5 years before diagnosis of idiopathic pulmonary fibrosis among newly diagnosed Medicare beneficiaries ($N = 7,306$)

	Year before Diagnosis when First Test Occurred										
	Fifth Year		Fourth Year		Third Year		Second Year		First Year*		
	No.	%	No.	%	No.	%	No.	%	No.	%	Cumulative %
Any diagnostic test	4,217	57.7	1,365	18.7	695	9.5	460	6.3	569	7.8	100.0
Pulmonary function testing	1,219	16.7	867	11.9	696	9.5	752	10.3	1,942	26.6	75.0
Chest radiograph	3,542	48.5	1,531	21.0	823	11.3	571	7.8	782	10.7	99.2
CT scan of the chest	1,399	19.1	978	13.4	864	11.8	962	13.2	3,103	42.5	100.0
Fiberoptic bronchoscopy	115	1.6	100	1.4	116	1.6	168	2.3	770	10.5	17.4
Autoimmune serologies	484	6.6	420	5.7	414	5.7	479	6.6	1,157	15.8	40.4
6-minute-walk test	142	1.9	127	1.7	156	2.1	229	3.1	742	10.2	19.1
Cardiopulmonary exercise testing†		N/A		N/A		N/A		N/A	33	0.5	1.1
Precipitin panel	22	0.3	26	0.4	26	0.4	47	0.6	244	3.3	5.0
Arterial blood gas	186	2.5	156	2.1	181	2.5	214	2.9	525	7.2	17.3
Oxygen saturation	753	10.3	600	8.2	566	7.7	618	8.5	1,176	16.1	50.8
Surgical lung biopsy	60	0.8	73	1.0	65	0.9	104	1.4	474	6.5	10.6
Pulmonologist visit	1,245	17.0	543	7.4	520	7.1	625	8.6	2,221	30.4	70.5

Definition of abbreviations: CT = computed tomography; N/A = not applicable.
*Including index date (the date of diagnosis of idiopathic pulmonary fibrosis).
†Four cell counts suppressed because of three cell sizes with counts less than 11.

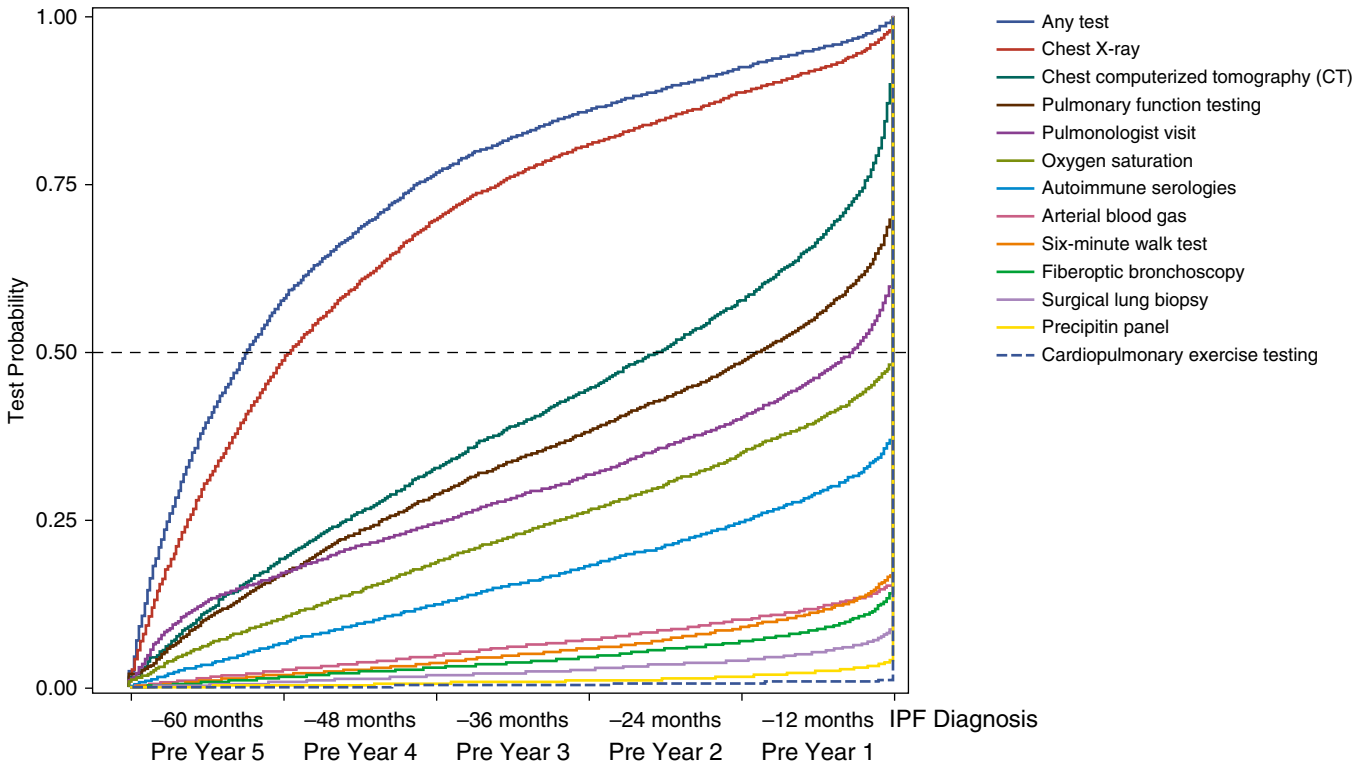

Figure 1. Cumulative probability curves illustrate the time from first recorded diagnostic test and first pulmonologist visit to diagnosis of idiopathic pulmonary fibrosis (IPF) among Medicare beneficiaries ($N = 7{,}306$).

patients, who predominated our study, may have been deferred (11, 12). Second, the long observation period pre-index could have introduced early testing that was unrelated to IPF diagnosis; we minimized this (immortal time) bias by including specialized testing that was likely related to a later diagnosis. Third, beneficiaries identified as having IPF may not have IPF, because of misclassification and/or miscoding (10, 13); however, our method for identifying IPF beneficiaries was derived from a modified code-based algorithm (10), with improved positive predictive value over prior algorithms. Finally, as an artifact of our study's 5-year look-back period, the final sample was older than typical beneficiaries with IPF.

Our study examined Medicare beneficiaries with IPF to show that diagnostic delays may occur, even after chest imaging, pulmonary function studies, and a pulmonologist's evaluation. Further study among ILD specialty centers and within the era of antifibrotic therapy may help confirm whether patients could be diagnosed earlier and if earlier diagnosis leads to improved clinical outcomes.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Joshua Mooney, M.D., M.S.
Stanford University
Stanford, California

Eunice Chang, Ph.D.
Partnership for Health Analytic Research, LLC
Beverly Hills, California

Deepa Lalla, Ph.D.
Palo Alto Outcomes Research
Palo Alto, California

Elya Papoyan, M.P.H.
Partnership for Health Analytic Research, LLC
Beverly Hills, California

Karina Raimundo, M.S.*
Genentech, Inc.
South San Francisco, California

Sheila R. Reddy, Ph.D., R.Ph.
Partnership for Health Analytic Research, LLC
Beverly Hills, California

John Stauffer, M.D.
Genentech, Inc.
South San Francisco, California

Tingjian Yan, Ph.D.
Michael S. Broder, M.D., M.S.H.S.
Partnership for Health Analytic Research, LLC
Beverly Hills, California

ORCID ID: 0000-0002-4687-194X (J.M.).

*Corresponding author (e-mail: raimundo.karina@gene.com).

References

1 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183:431–440.
2 Oldham JM, Noth I. Idiopathic pulmonary fibrosis: early detection and referral. *Respir Med* 2014;108:819–829.

3 Nathan SD, Shlobin OA, Weir N, Ahmad S, Kaldjob JM, Battle E, *et al*. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. *Chest* 2011;140:221–229.
4 Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clin Epidemiol* 2013;5:483–492.
5 Wells AU, Costabel U, Poletti V, Crestani B, Egan J, Margaritopoulos G, *et al*. Challenges in IPF diagnosis, current management and future perspectives. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32:28–35.
6 Cosgrove GP, Bianchi P, Danese S, Lederer DJ. Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey. *BMC Pulm Med* 2018;18:9.
7 Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am J Respir Crit Care Med* 2011;184:842–847.
8 Raghu G, Chen S-Y, Hou Q, Yeh W-S, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. *Eur Respir J* 2016;48:179–186.
9 Raghu G, Chen S-Y, Yeh W-S, Maroni B, Li Q, Lee YC, *et al*. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med* 2014;2:566–572.
10 Ley B, Urbania T, Husson G, Vittinghoff E, Brush DR, Eisner MD, *et al*. Code-based diagnostic algorithms for idiopathic pulmonary fibrosis. case validation and improvement. *Ann Am Thorac Soc* 2017;14:880–887.
11 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
12 Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016;193:1161–1167.
13 Esposito DB, Lanes S, Donneyong M, Holick CN, Lasky JA, Lederer D, *et al*. Idiopathic pulmonary fibrosis in United States automated claims. incidence, prevalence, and algorithm validation. *Am J Respir Crit Care Med* 2015;192:1200–1207.

Ethics of Health Research Supported by For-Profit Cannabis Companies: What Have We Learned from Big Tobacco?

To the Editor:

As clinician-investigators with an interest in the impact of legalized cannabis on pulmonary diseases, we read the results of a clinical trial of vaporized cannabis for advanced chronic obstructive pulmonary disease with enthusiasm (1). We commend the researchers for conducting a well-designed study focused on use of noncombusted cannabis for pulmonary conditions. However, publication of this study by *AnnalsATS* raises an important point. Together with acknowledging support of the study's authors by numerous funding sources, including the Canadian Institutes of Health Research, the senior author also received an investigator-initiated study grant from Tilray. Per the company's website, (www.tilray.com), "Tilray is a global leader in medical cannabis research, cultivation, processing and distribution [that aspires] to lead, legitimize and define the future of our industry by building the world's most trusted cannabis company.… [W]e are the first GMP-certified medical cannabis producer to supply cannabis flower and extract products to tens of thousands of patients, physicians, pharmacies, hospitals, governments and researchers.…" Tilray was listed on the Nasdaq Stock Market (NASDAQ:TLRY) in July 2018 with a market value reportedly worth $5 billion (2), making it relatively smaller than Philip Morris International or Coca-Cola, each valued at over $100 billion. However, Tilray's involvement in the study begs the question: Is it ethical to accept a study for publication that has been supported by for-profit cannabis corporations whose products have an unknown and potentially negative impact on human health?

All three journals under the aegis of the American Thoracic Society (ATS) provide clearly stated policies for authors regarding work supported by the tobacco industry, namely that authors must certify that no part of the research presented has been funded by tobacco industry sources, similar to many other medical journals. Importantly, for none of the ATS-affiliated journals, nor for any other major medical journals, is cannabis industry funding for research queried specifically in the authors' instructions, despite the fact that consuming cannabis by combustion remains most common among regular users (3).

Accepting funding from commercial sources to conduct research has the potential to bias scientific investigations and may also undermine trust in research results. Tobacco industry research funding is the most obvious example in which strategies used by the industry to shape evidence on risk have been identified, including funding and publishing research that supports the interest group's position (4). Earlier this year, alcohol industry support of federal research regarding alcohol use also came under similar scrutiny when the National Institutes of Health (NIH) stopped a $100 million study of the putative benefits of alcohol on human health that was revealed to be largely supported by the alcohol industry, which may have had input during the trial's design in 2013 and 2014 (5).

Although conducting clinical trials related to cannabis in the United States remains challenging, options do exist for performing this type of work that do not require direct funding from industry. Methods that investigators have used include purchasing cannabis from a commercial supplier using investigator funding (including suppliers in Good Manufacturing Practice–certified facilities [6]) or using cannabis supplied for research purposes free of charge (less optimal). The National Institute on Drug Abuse also has a drug supply program that can provide both NIH-sponsored and non–NIH-sponsored investigators with cannabis products for research after an Investigational New Drug Application is filed and reviewed and a Drug Enforcement Administration registration for cannabis (a schedule I controlled substance) is obtained by the investigator. We hope that editors of ATS journals will urgently clarify instructions with respect to investigators accepting funding from for-profit cannabis companies with the same level of concern as tobacco industry–funded investigations until sufficient evidence can be provided regarding its safety for human health.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ellen L. Burnham, M.D.*
University of Colorado School of Medicine
Aurora, Colorado