otherwise) to emerge from the shadows and obtain coverage is largely contingent on the perceived political and legal climate. Earlier this year, Republican Congressional leaders attempted, ultimately unsuccessfully, to tie funding for the Department of Homeland Security to the dismantlement of the program. Meanwhile, the decision by a federal judge to temporarily halt the policy in response to a lawsuit filed by 26 states raises the possibility that the program's fate will end up being decided by the Supreme Court. These uncertainties may leave many immigrants reluctant to come forward and seek coverage. And any gains may be ephemeral if the policy is ultimately reversed by the courts, legislative action, or a future President.

An audio interview with Dr. Sommers is available at NEJM.org

Overall, the President's policy — if implemented — is likely to increase insurance coverage in immigrant communities. Nevertheless, most undocumented immigrants in the United States will remain significantly limited in their ability to obtain health insurance and to access needed health care.[2] Beyond the surrounding legal and political controversies, this executive action is no substitute for a comprehensive immigration-reform law that addresses the health needs of immigrants. Given the gridlock in Washington, D.C., however, such a law seems an improbable aspiration.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Capps R, Bachmeier JD, Fix M, Van Hook J. A demographic, socioeconomic, and health coverage profile of unauthorized immigrants in the United States. Washington, DC: Migration Policy Institute, May 2013.
2. Bustamante AV, Chen J. Health expenditure dynamics and years of U.S. residence: analyzing spending disparities among Latinos by citizenship/nativity status. Health Serv Res 2012;47:794-818.
3. Tumulty K. Illegal immigrants could receive Social Security, Medicare under Obama action. Washington Post. November 25, 2014 (http://www.washingtonpost.com/politics/illegal-immigrants-could-receive-social-security-medicare-under-obama-action/2014/11/25/571caefe-74d4-11e4-bd1b-03009bd3e984_story.html).
4. Sommers BD, Tomasi MR, Swartz K, Epstein AM. Reasons for the wide variation in Medicaid participation rates among states hold lessons for coverage expansion in 2014. Health Aff (Millwood) 2012;31:909-19. [Errata, Health Aff (Millwood) 2012;31:1650, 2831.]
5. Watson T. Inside the refrigerator: immigration enforcement and chilling effects in Medicaid participation. Cambridge, MA: National Bureau of Economic Research, August 2010.

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Forced Vital Capacity in Idiopathic Pulmonary Fibrosis — FDA Review of Pirfenidone and Nintedanib

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Idiopathic pulmonary fibrosis (IPF) is a devastating disease of unknown cause, and for years the only effective treatment available was lung transplantation. In October 2014, two drugs became available in the United States for patients with IPF when the Food and Drug Administration (FDA) approved pirfenidone (Esbriet, InterMune) and nintedanib (Ofev, Boehringer Ingelheim).[1] Both drugs posed a similar regulatory challenge, in that the primary efficacy variable studied in both cases was the change in forced vital capacity (FVC). FVC, a measure of lung function, had not been established as a surrogate for clinically meaningful benefit in IPF.

Pirfenidone, a pyridone, is thought to act through anti-inflammatory and antifibrotic pathways, although its exact mechanism is unknown. The FDA had declined to approve an initial marketing application for pirfenidone in a first review cycle in 2010. At that time, two 72-week studies were submitted for review. Their primary efficacy variable was the absolute change in the percentage of the predicted FVC from baseline to week 72. In one study, pirfenidone had not been shown to have a significantly greater effect than placebo on that measure. At the time of the agency's decision not to approve pirfenidone, outside experts, including many members of the Pulmonary–Allergy Drugs Advisory Committee convened in May 2010, supported that decision.[1,2]

Before resubmitting its marketing application in 2014, the sponsor conducted a new 52-week study in which the primary efficacy end point — a decline in FVC from baseline to week 52 that was significantly smaller than that in the placebo group — was met. With two studies demonstrating a statistically significant effect on FVC and providing supportive evidence regard-

Analysis of Forced Vital Capacity and All-Cause Mortality.*

Study	Forced Vital Capacity			All-Cause Mortality		
	Change from Baseline (ml)		Treatment Difference (95% CI)	No. of Deaths (%)		Hazard Ratio for Time to Death (95% CI)
	study drug	*placebo*		*study drug*	*placebo*	
Pirfenidone study 2 (November 2008)	−318	−475	157 (3 to 311)	14 (8.0)	20 (11.5)	0.65 (0.33 to 1.29)
Pirfenidone study 3 (November 2008)	−379	−373	−6 (−178 to 167)	18 (10.5)	17 (9.8)	1.07 (0.55 to 2.08)
Pirfenidone study 1 (re-submitted; February 2014)	−235	−428	193 (96 to 289)	12 (4.3)	21 (7.6)	0.57 (0.28 to 1.16)
Nintedanib study 1 (June 2010)	−60	−191	131 (27 to 235)	7 (8.1)	9 (10.3)	0.73 (0.27 to 1.98)
Nintedanib study 2 (October 2013)	−115	−240	125 (78 to 173)	13 (4.2)	13 (6.4)	0.63 (0.29 to 1.36)
Nintedanib study 3 (October 2013)	−114	−207	94 (45 to 143)	22 (6.7)	20 (9.1)	0.74 (0.40 to 1.35)

* The studies are listed in chronologic order by drug, with study numbers as referenced in the product labels and the months in which enrollment ended. Data for forced vital capacity are the absolute values for the change from baseline to week 52 for pirfenidone study 1, to week 72 for pirfenidone studies 2 and 3, and to week 52 for all nintedanib studies; the change from baseline for pirfenidone studies was based on descriptive statistics, and the change from baseline for nintedanib studies was based on regression analysis. Mortality data are from the vital status analysis (from randomization to the time of death) and include all deaths irrespective of the cause and of whether the patient had continued treatment. Hazard ratios for time to death are based on Cox proportional-hazards regression analysis. CI denotes confidence interval.

ing important secondary efficacy variables, including mortality, pirfenidone was approved during this second review cycle.

Nintedanib, a tyrosine kinase inhibitor, was approved in its first review cycle in 2014. The clinical development program consisted of three 52-week studies whose primary efficacy variable was the annual rate of FVC decline. In all three studies, the primary efficacy end point was achieved. The benefit with respect to decline in FVC was supported by results for secondary variables including time to IPF exacerbation and mortality.

Both drugs were approved on the basis of slowed decline in FVC. The efficacy variable that would be most clinically meaningful and useful for IPF clinical development programs has been an ongoing topic of discussion both within and outside the FDA. Use of FVC as an efficacy measure has been both supported and discouraged in the literature.[3] Given that IPF causes a progressive decline in pulmonary function in a restrictive, or scarring, pattern, it seems logical to monitor for a change in a lung-function parameter such as FVC that reflects such changes. But the threshold for a clinically meaningful decline in FVC is uncertain, and the variable had not been validated as a surrogate for likelihood of death or other clinically meaningful efficacy variables in IPF. Some studies had revealed a correlation between FVC decline and mortality, but the lack of an effective IPF therapy had precluded validation of FVC as a surrogate for mortality or other clinically meaningful end points.[4] Without a therapy known to provide a clinically meaningful benefit, there was no benchmark against which to validate FVC decline.

These uncertainties regarding FVC contributed to the decision not to approve pirfenidone in the first review cycle.[1] In the absence of a valid surrogate or biomarker for a clinically meaningful measure of efficacy, the FDA took the position that an effect on mortality would be the most unequivocal and clinically important measure of efficacy against this progressive and ultimately fatal disease.[1] Academic and industry experts, however, asserted that it was impractical to design studies to examine mortality among patients with IPF, given the large number of patients and long duration that would be required. The FDA was therefore persuaded to accept study designs using FVC decline as the primary efficacy variable.

Because of the uncertainties regarding FVC, however, the FDA emphasized that other clinically important measures of efficacy,

including mortality, should be used to provide supportive evidence that a drug had affected the disease. In reviewing the marketing applications for pirfenidone and nintedanib, the agency then carefully considered the studies' evaluation of mortality. Although the cause of death was adjudicated in some of the studies, given the difficulty of distinguishing between respiratory and other causes of death, such as cardiovascular disease or infection, and because deaths were expected to be predominantly related to IPF, the FDA considered all-cause mortality the most appropriate variable for analysis.

The timing of deaths in relation to treatment was also considered carefully. On-treatment analysis of mortality (the rate of deaths occurring between randomization and a specified time point after the last dose of drug is administered) has generally been used to inform assessments of a drug's safety, whereas vital status analysis (assessing the time from randomization to death, irrespective of the cause of death and of whether patients had continued receiving treatment) has been seen as more informative regarding a drug's efficacy. Although the FDA analyzed both types of mortality data in the cases of nintedanib and pirfenidone, it relied on the vital status analysis in assessing the drugs' efficacy with respect to mortality.

Because of the correlation between FVC and mortality among patients with IPF, the FDA also considered the relationship between FVC and mortality in the studies of pirfenidone and nintedanib (see table). In five of those six studies, FVC declined significantly less in patients who received pirfenidone or nintedanib than in those given placebo. Although none of the individual studies were powered to demonstrate a statistically significant reduction in mortality in a vital status analysis, in the five studies that revealed a significant difference in FVC decline, there was a numerical trend toward improvement in mortality (hazard ratios <1). Conversely, in the one study in which there was no difference between treatment groups in FVC decline (pirfenidone study 3), there was also no numerical trend suggesting a mortality benefit.

Thanks to these studies, we now have more data on the relationship between FVC and mortality among patients with IPF. Undoubtedly, the approval of pirfenidone in the second review cycle, 4 years after the original FDA submission, raises the question in some people's minds of whether the delay in approval was justified. Pirfenidone had been approved in Japan on the basis of the same data that led to the FDA's denial of approval. From the FDA's perspective, neither the efficacy of pirfenidone in terms of FVC decline nor the validity of that variable as a measure of clinical benefit was clear. The third pirfenidone study and the completed nintedanib clinical development program provided invaluable data for IPF-drug development and evaluation, since the studies that showed a benefit in terms of FVC decline also showed a trend toward decreased mortality. Although it was coincidental that the FDA had the opportunity to review these two drugs simultaneously, the relationship between FVC and mortality trends in both sets of clinical trials strengthened our ability to rely on FVC as a clinically relevant efficacy measure in IPF.

The unmet need for therapies for IPF has always been recognized by the FDA. But the demonstration of efficacy through critical analysis of the data was a prerequisite to approval; after all, approving an ineffective drug does a disservice to both patients and science.

Now, patients with IPF have two effective drugs available. Interesting questions remain, including whether the drugs will be used in combination and whether such use might provide incremental benefit over monotherapy. Given the drugs' individual effects on mortality trends, answering such a research question may be an important pursuit for the academic community.

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1. Food and Drug Administration. Drugs@FDA: FDA approved drug products (http://www.accessdata.fda.gov/scripts/cder/drugsatfda).
2. Karimi-Shah BA. Pulmonary-Allergy Drugs Advisory Committee meeting: pirfenidone capsules NDA 22-535, S-000. Silver Spring, MD: Food and Drug Administration, March 9, 2010 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PulmonaryAllergyDrugsAdvisoryCommittee/UCM206398.pdf).
3. Raghu G, Collard HR, Anstrom KJ, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012;185:1044-8.
4. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538-42.

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