Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Health Aff (Millwood). Author manuscript; available in PMC 2018 July 10.

Published in final edited form as:

Health Aff (Millwood). 2018 May ; 37(5): 773–779. doi:10.1377/hlthaff.2017.1554.

Precision Medicine In Action: The Impact Of Ivacaftor On Cystic Fibrosis–Related Hospitalizations

Lisa B. Feng,
Senior director for policy and advocacy at the Cystic Fibrosis Foundation, in Bethesda, Maryland

Scott D. Grosse,
Research economist at the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia

Ridgely Fisk Green,
Carter Consulting, Inc. contractor in the Office of Public Health Genomics, CDC

Aliza K. Fink, and
Director of epidemiology at the Cystic Fibrosis Foundation

Gregory S. Sawicki
Assistant professor of pulmonology at Boston Children's Hospital, in Massachusetts

Abstract

Cystic fibrosis is a life-threatening genetic disease that causes severe damage to the lungs. Ivacaftor, the first drug that targeted the underlying defect of the disease caused by specific mutations, is a sterling example of the potential of precision medicine. Clinical trial and registry studies showed that ivacaftor improved outcomes and reduced hospitalizations. Our study used US administrative claims data to assess the real-world effectiveness of ivacaftor. Comparing twelve-month rates before and after starting the use of ivacaftor among people who initiated therapy during 2012–2015, we found that overall and cystic fibrosis–related inpatient admissions fell by 55 percent and 81 percent, respectively. There was a comparable reduction in inpatient spending. Ivacaftor appears to be effective for multiple mutations that cause the disease, as suggested by the fact that during the study period, ivacaftor's use was extended to nine additional mutations in 2014. Examination of evidence from clinical trial, clinical care, and administrative data sources is important for understanding the real-world effectiveness of precision medicines such as ivacaftor.

Cystic fibrosis is a life-threatening genetic disease that affects approximately 35,000 people in the United States.[1] Advances in genetically targeted therapies have brought hope for people with the disease.[2–5] Cystic fibrosis is caused by the absence or reduced function of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that regulates salt and water balance on the surface of cells and is encoded by the *CFTR* gene.[6] Progressive airway destruction, characterized by chronic lung infections and loss of lung function, is the predominant cause of morbidity and mortality.[7] Ivacaftor (brand name Kalydeco), a small-molecule drug approved by the Food and Drug Administration (FDA) in January 2012, was the first therapy that addressed the CFTR defect among people six years old and older with a *G551D CFTR* gene variant, a mutation present in 3–4 percent of the population with cystic

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

fibrosis.[8] While not a cure, ivacaftor is the first drug to treat the CFTR abnormality instead of treating the symptoms.[9]

Ivacaftor exemplifies the promise of precision medicine: delivering better health outcomes by treating people based on their unique genetic makeup.[10,11] Some observers doubt that precision medicine can fulfill its promise, specifically citing ivacaftor and noting that impressive gains in cystic fibrosis patients' survival in recent decades have been achieved through strict adherence to clinical guidelines, not genomics.[12] Indeed, the median predicted survival age in the United States rose from twenty-nine years for people born in 1986–90 to forty-three years for those born in 2012–16.[7] However, the criticism overlooks limited progress in reducing pulmonary morbidity, which is targeted by therapies such as ivacaftor.[7,13] Clinical trials of ivacaftor have shown major improvements, including a 55 percent reduced risk of pulmonary exacerbation, which is an acute worsening of lung disease that typically requires treatment with antibiotics.[13] The drug was also associated with improved weight gain and quality of life.[14,15] Two observational studies have confirmed ivacaftor's real-world effectiveness: A patient registry study found that lung function declined more slowly among patients using ivacaftor, compared to a control group receiving standard care; and an analysis of private insurance claims found lower rates of hospitalization.[16,17]

Not surprisingly, uptake of ivacaftor was rapid: 80 percent of eligible patients were on the drug within the first twelve months of the FDA's approval in January 2012.[18] The FDA expanded the label to include nine additional mutations that cause defects in the CFTR protein similar to the *G551D* variant in 2014, and to twenty-eight more mutations in 2017.[19] (See online appendix exhibit A1 for decision dates and a list of mutations.)[20] The label expansions more than tripled eligibility, to 14 percent of the cystic fibrosis population. Listed at $311,000 per year, ivacaftor is covered by most US public and commercial payers. Though the drug is indeed costly compared to ibuprofen, as noted by critics,[12] it is vastly more effective in managing respiratory complications of cystic fibrosis.

Using real-world data to generate evidence on the effectiveness of precision medicines such as ivacaftor is important for patients, clinicians, and payers, as eligibility for the drug expands by patients' age and genetic mutation. Our analysis builds upon previous studies by estimating all-cause and cystic fibrosis–related hospitalizations one year before and one year after the initiation of ivacaftor among patients who began treatment during February 2012–December 2015—a period that included the two label expansions in 2014.We also estimated hospitalization rates by patient age group and medication adherence—factors that may modify the magnitude of treatment response.

Study Data And Methods

DATA SOURCE

We analyzed administrative claims data from the Truven Health Analytics MarketScan Commercial Research Database, which contains information on tens of millions of people with employer-sponsored insurance from a sample of US private health plans provided through employers. We accessed the MarketScan data via version 4.0 of Treatment Pathways, an online analytic platform that includes data from both the MarketScan

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Commercial and MarketScan Medicare Supplemental databases, restricted to health plans with prescription drug benefits. The analysis used MarketScan data on people younger than sixty-five years old from January 1, 2010, through December 31, 2016.

People were eligible for our analysis if they had an *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), or *International Statistical Classification of Diseases and Related Health Problems* (ICD-10-CM) diagnosis code for cystic fibrosis on one or more inpatient claims or on two or more outpatient claims (excluding laboratory claims) at least thirty days apart. In addition, they needed to have at least one prescription claim for ivacaftor monotherapy, be at least six years old at the time of the first filled prescription, and have twelve months of continuous enrollment before and after their first filled prescription.

ANALYSIS

The study was designed so that people with cystic fibrosis who took ivacaftor were their own controls. The pre-ivacaftor period was the twelve months before a person's first filled prescription, and the post-ivacaftor period was the twelve months after the first filled prescription. During each period we calculated the numbers and percentages in each group of people with one or more hospitalization for any reason and those with one or more hospitalizations for which cystic fibrosis was listed as the principal diagnosis.We also calculated the rates of all hospitalizations and those related to cystic fibrosis as numbers of admissions per person-year.

The percentage reductions between the pre- and post-ivacaftor periods were calculated as 1 minus the ratio of percentages or rates. We assessed the significance of the differences in proportions by performing McNemar's one-tailed test of paired sample proportions using exact binomial probability calculations and a p value of 0.05.

In addition to analysis of the whole cohort, we separately analyzed data for two subcohorts: the eighty-six people who started using ivacaftor in the period February 6, 2012–February 21, 2014, under the initial FDA label; and the fifty-seven people who initiated use of ivacaftor in the period February 22, 2014–December 31, 2015, under the expanded FDA label. Including claims through the end of 2015 gave us twelve months of follow-up on inpatient admissions with fully adjudicated claims data through the end of 2016.

We tested the hypothesis of similarity of treatment effects in the two cohorts. Because of the high uptake rate (80 percent after twelve months of approval) of ivacaftor previously observed in people with *G551D* mutations,[18] we assumed that the second cohort consisted mostly of people without a *G551D* mutation. Our tabulation of data from the Cystic Fibrosis Foundation Patient Registry confirmed that more than 80 percent of patients who initiated use of ivacaftor during 2014 or 2015 did not have a *G551D* mutation, compared with 11 percent of those who first took ivacaftor during 2012 or 2013.

To address the potential impact of medication adherence, we distinguished two groups of ivacaftor users based on their number of prescription fills during the twelve months beginning with the first fill: people who had 3–9 fills and those who had 10–12 fills.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Standard prescribing for ivacaftor entails a prescription filled every twenty-eight days. It is standard practice to define adherence as a minimum medication possession ratio of 80 percent over a defined time period.[21,22] For a standard prescription, a minimum medication possession ratio of 80 percent corresponds to ten fills in a twelve-month period. Six (4 percent) patients with just 1–2 fills were excluded from the adherence analysis.

Finally, we calculated the pre-post change in mean per patient twelve-month spending for inpatient services to estimate the cost offset associated with use of ivacaftor. We adjusted spending for medical inflation.

LIMITATIONS AND CRITICAL ASSUMPTIONS

Like any study using administrative claims data, ours had limitations. First, MarketScan Commercial data consist of a convenience sample of people with employer-sponsored insurance, and our results are not generalizable to people with public insurance or the uninsured. However, we were able to replicate the analysis with a MarketScan Medicaid sample.

Second, there may be errors or inconsistencies in diagnosis codes used to identify cystic fibrosis, although this limitation is mitigated by the fact that the analysis included only people on ivacaftor.

Third, information on inpatient admissions may be incomplete. For example, hospitalizations might not have been coded with a diagnosis of cystic fibrosis.

This study also included some critical assumptions. We assumed that most people on ivacaftor in both cohorts had eligible mutations listed on the label. In other words, we did not account for off-label use. We were also unable to classify results by mutation, because administrative data do not record mutation status and we were unable to link individuals in this analysis to patients included in the Cystic Fibrosis Foundation Patient Registry. Finally, since administrative data do not include clinical measures, we were unable to account for disease severity.

Study Results

The total sample included 143 people who had filled prescriptions for ivacaftor, 63 percent of whom were age eighteen or older (exhibit 1). In the year before filling their first prescription for ivacaftor, 31 percent of patients had had at least one inpatient admission. Overall, the rate of inpatient admissions decreased 55 percent, from 0.57 admissions per person-year in the period before filling the first prescription to 0.26 admissions in the period after filling that prescription. Decreases were similar for children and adults (59 percent and 52 percent, respectively).

The percentages of people with one or more admissions also decreased over time by 55 percent ($p < 0{:}0001$). Similar to the decreases in admission rates, the change in the percentages of people with one or more admissions was not significantly different between age groups, with a 61 percent decrease for children ($p = 0{:}0096$) and a 50 percent decrease for adults ($p = 0{:}0033$).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Admissions related to cystic fibrosis, a subset of all-cause admissions, decreased even more dramatically than all-cause admissions did. The percentages of people with one or more admissions with a principal diagnosis of cystic fibrosis decreased by 78 percent overall ($p <$ 0:0001). Admissions with principal diagnosis codes for cystic fibrosis decreased from forty-two before filling a prescription for ivacaftor to eight after filling that prescription—an 81 percent reduction. Rates per person per year decreased by 82 percent among children ages 6–17 and 80 percent among adults. The decreases in the percentages of people with one or more admissions were also similar between age groups, with declines of 80 percent for children and 77 percent for adults.

The declines in the percentages of people with one or more admissions were similar between the initial and expanded-label subcohorts, with declines in overall admissions of 59 percent and 57 percent and decreases in admission rates of 49 percent and 62 percent, respectively. (See appendix exhibit A2 for subcohort analyses of inpatient admissions before and after initiating use of ivacaftor.)[20]

Exhibit 2 shows the association of medication adherence with all-cause inpatient admissions. Because of small numbers, we did not report analyses stratified by age or analyses of cystic fibrosis–specific admissions. Patients who filled at least 10 prescriptions during the twelve-month period experienced 68 percent pre-post reductions in inpatient admissions, compared with 45 percent for those with 3–9 fills.

Use of ivacaftor was associated with 60 percent lower per person inpatient spending (adjusted for medical inflation to 2016 prices) in the year following initiation, relative to the year preceding it. There was a greater proportional reduction in hospital costs for adults taking ivacaftor than for children (68 percent and 45 percent, respectively), but similar absolute differences. There was an absolute per person reduction of $10,567, from $17,729 to $7,162 (exhibit 3).

Discussion

Ivacaftor serves as a sterling example of precision medicine in that it effectively treats a subpopulation of people with cystic fibrosis based on their unique genetic makeup. Our analysis of administrative claims data confirmed the association of ivacaftor with reduced hospitalizations that was initially reported in clinical trial and patient registry studies.[13–17] We were able to account for medication adherence and found greater reductions in hospitalizations among those who were adherent to treatment. Our findings showed similar effectiveness for ivacaftor following the FDA label expansion, which suggests that including additional mutations did not lower the drug's effectiveness.

Our findings and those of others[13–17] suggest that sustained use of ivacaftor can markedly reduce overall hospitalizations, especially those related to cystic fibrosis. For people who initiated the use of ivacaftor in the period February 6, 2012–December 31, 2015, overall hospital admissions fell by approximately 55 percent, and those related to cystic fibrosis fell by 81 percent. A similar analysis showed decreases of 40 percent for all inpatient admissions and 75 percent for cystic fibrosis–related admissions.[16] These reductions are significant

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

since inpatient rates have not improved in recent years, despite gains in survival that have resulted from improvements in standards of care for patients with cystic fibrosis. The Cystic Fibrosis Foundation Patient Registry estimates that 33–34 percent of people with cystic fibrosis were hospitalized for lung infections between 2010 and 2014.[7] Analyses of Marketscan data showed that inpatient rates decreased by only 1 percent per year among people not on ivacaftor (data not shown).

We observed modestly greater reductions in all-cause admissions for pediatric patients compared to adults, but the declines were not significantly different between the two age groups. Adult and pediatric patients experienced similar rates of hospitalization after beginning the use of ivacaftor. Combined with the evidence that ivacaftor slows the rate of decline of lung function, our analysis appears to support initiation of ivacaftor at an early age to maximize its therapeutic benefits.

These findings apply to the population with private employer-sponsored insurance. Most people with cystic fibrosis have some kind of insurance, with 44 percent on Medicaid as of 2016.[7] Prior evidence suggests that people with the disease on Medicaid experience worse health outcomes, compared to those with private insurance.[23] We repeated our analysis with a Medicaid sample and found smaller reductions in inpatient admissions (38 percent for all-cause and 46 percent for cystic fibrosis–related admissions), compared to the reductions experienced by the privately insured. (See appendix exhibit A3 for our analysis of the Medicaid sample.)[20] Among people with one or more ivacaftor prescription fills, Medicaid enrollees were three times more likely to be highly nonadherent (filling only 1–2 prescriptions in twelve months). We do not have further insight on confounding factors that could contribute to these differences beyond Medicaid enrollment. We do know from our analysis that the proportion of patients with cystic fibrosis on Medicaid with a filled prescription for ivacaftor was much lower than the proportion in the private-payer sample. Future studies should investigate the role that health insurance type plays in the association between access to precision medicines and health outcomes, adjusting for broader socioeconomic issues such as transportation, housing, employment, and food insecurity.

Ivacaftor is covered by private and public payers in the United States. The drug is also available in Canada, Australia, and European countries, which have different processes for covering drugs than the US does.[24,25] Payers that cover ivacaftor have implicitly accepted the drug's value, or at least accepted its budget impact. However, the ability of health plans, states, and countries to afford additional specialty therapies with growing patient populations is the subject of an ongoing debate. Cost concerns can lead to access delays. For example, Ireland's national health payer did not approve reimbursement for ivacaftor until 2013, to allow for additional time for price negotiation.[24] Payers also address cost concerns by shifting costs to patients via copayments and coinsurance, which can create financial barriers to access for patients. Our data showed an average offset of $10,000 (2016 dollars) from the reduced hospitalizations after patients started to use ivacaftor. Although this is a small proportion of the $311,000 list price of ivacaftor, we do not know how much payers actually paid for the drug. Additionally, calculations of cost-effectiveness require the use of measures beyond reduced utilization, such as productivity and quality of life for patients and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

caregivers. Since precision medicine, by definition, is not meant to be marketed to broad populations, issues of affordability and proposed policy solutions will continue to arise.

This study provides real-world evidence that use of ivacaftor following the extension of the FDA label to an additional nine mutations in 2014 was associated with effectiveness similar to what it had following the initial approval in 2012. Developing treatments for all people with cystic fibrosis, however, is challenging since there are approximately 1,700 *CFTR* mutations.[26] Designing clinical trials for every mutation becomes impractical or impossible because of very small numbers and wide geographic dispersion. Thus, in vitro cell lines that express *CFTR* of rare variants have been used to test the effect of therapeutic compounds.[27] In fact, in May 2017 the FDA used this novel approach to approve the use of ivacaftor for an additional twenty-three mutations, extending eligibility to an additional 3 percent of people with cystic fibrosis in the US, for a total of 16 percent able to use the drug.[28,29] This in vitro process creates a drug development and regulatory pathway for assessing the clinical benefit of rare mutations that are not conducive to clinical trials.[27,28] The FDA's recognition that non-clinical-trial data are sufficient to demonstrate efficacy is especially significant for precision medicine, where the goal is to deliver individualized treatments. While the FDA expands its use of data sources for approval based on safety and efficacy standards, payers have to make decisions based on effectiveness and cost. Greater alignment in and agreement on the use of real-world evidence for regulatory and payment purposes will become increasingly important as new precision medicines are developed and assessed with new techniques.

Treatments that target the protein defect that causes cystic fibrosis illustrate the promise of precision medicine. While it is unlikely that the percentage of cystic fibrosis patients eligible for ivacaftor will increase much more, new drugs, such as a combination of ivacaftor and lumacaftor (Orkambi) therapy, that target different *CFTR* variants have FDA approval, and more are in the pipeline.[5] Understanding the real-world effectiveness of ivacaftor and similar therapies requires the examination of evidence from clinical trial, clinical care, and administrative data sources.[30] Despite data limitations, real-world evidence of effectiveness, as summarized here, can help providers, policy makers, and patients assess the value of treatments relative to their cost and use. Finally, it is important to acknowledge that cystic fibrosis precision medicine is not just about genomics. To deliver the right care to the right patient, cystic fibrosis care must continue to account for other aspects unique to individuals such as environment, physiology, patients' preferences, and lifestyle. ■

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Muin Khoury provided helpful comments on a previous version of the article.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

NOTES

1. Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, et al. The Cystic Fibrosis Foundation Patient Registry. Design and methods of a national observational disease registry. Ann Am Thorac Soc. 2016; 13(7):1173–9. [PubMed: 27078236]
2. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015; 372(9):793–5. [PubMed: 25635347]
3. Marson FAL, Bertuzzo CS, Ribeiro JD. Personalized or precision medicine? The example of cystic fibrosis. Front Pharmacol. 2017; 8:390. [PubMed: 28676762]
4. Martiniano SL, Sagel SD, Zemanick ET. Cystic fibrosis: a model system for precision medicine. Curr Opin Pediatr. 2016; 28(3):312–7. [PubMed: 27031658]
5. Paranjape SM, Mogayzel PJ Jr. Cystic fibrosis in the era of precision medicine. Paediatr Respir Rev. 2018; 25:64–72. [PubMed: 28372929]
6. Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. Nat Med. 2012; 18(4): 509–19. [PubMed: 22481418]
7. Cystic Fibrosis FoundationPatient Registry: annual data report [Internet]Vol. 2017. Bethesda (MD): The Foundation; 2016[cited 2018 Feb, 26]. Available from: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf
8. Vertex [Internet]Boston (MA): Vertex; 2012Press release, FDA approves Kalydeco™ (ivacaftor), the first medicine to treat the underlying cause of cystic fibrosis; 2012 Jan 31[cited 2018 Feb 26]. Available from: http://investors.vrtx.com/releasedetail.cfm?releaseid=644257
9. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016; 4(8): 662–74. [PubMed: 27053340]
10. Herper, M. The most important new drug of 2012. Forbes [serial on the Internet]2012Dec 27. [cited 2018 Feb 26]. Available from: https://www.forbes.com/sites/matthewherper/2012/12/27/the-most-important-new-drug-of-2012/#40ad3bfb3a6a
11. Cystic Fibrosis FoundationPresident Obama highlights cystic fibrosis in 2015 State of the Union address [Internet]Bethesda (MD): Cystic Fibrosis Foundation; 2015Jan 21. [cited 2018 Feb 26]. Available from: https://www.cff.org/News/News-Archive/2015/President-Obama-Highlights-Cystic-Fibrosis-in-2015-State-of-the-Union-Address/
12. Joyner MJ, Paneth N. Seven questions for personalized medicine. JAMA. 2015; 314(10):999–1000. [PubMed: 26098474]
13. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011; 365(18):1663–72. [PubMed: 22047557]
14. Quittner A, Suthoff E, Rendas-Baum R, Bayliss MS, Sermet-Gaudelus I, Castiglione B, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. Health Qual Life Outcomes. 2015; 13:93. [PubMed: 26135562]
15. Edgeworth D, Keating D, Ellis M, Button B, Williams E, Clark D, et al. Improvement in exercise duration, lung function, and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. Clin Sci (Lond). 2017; 131(15): 2037–45. [PubMed: 28611235]
16. Suthoff ED, Bonafede M, Limone B, O'Callaghan L, Sawicki GS, Wagener JS. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. J Med Econ. 2016; 19(9):845–51. [PubMed: 27074519]
17. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and Cystic Fibrosis Patient Registry data. Am J Respir Crit Care Med. 2015; 192(7):836–42. [PubMed: 26132840]
18. Sawicki GS, Dasenbrook E, Fink AK, Schechter MS. Rate of uptake of ivacaftor use after U.S. Food and Drug Administration approval among patients enrolled in the U.S. Cystic Fibrosis Foundation Patient Registry. Ann Am Thorac Soc. 2015; 12(8):1146–52. [PubMed: 26073026]
19. Vertex [Internet]Boston (MA): Vertex; 2017Press release, FDA approves KALYDECO® (ivacaftor) for more than 600 people ages 2 and older with cystic fibrosis who have certain residual function

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

mutations; 2017 Aug 1 [cited 2018 Feb 26]. Available from: http://investors.vrtx.com//releasedetail.cfm?ReleaseID=1035299

20. To access the appendix, click on the Details tab of the article online.
21. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006; 40(7–8):1280–8. [PubMed: 16868217]
22. Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. J Cyst Fibros. 2011; 10(4): 258–64. [PubMed: 21458391]
23. Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, et al. Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. Ann Intern Med. 2017; 166(8):537–46. [PubMed: 28288488]
24. Corcoran A, Hickey N, Barry M, Usher C, McCullagh LM. Ivacaftor for cystic fibrosis: an evaluation of real world utilisation and expenditure in the Irish Healthcare Setting. Ir Med J. 2017; 110(7):619. [PubMed: 29169001]
25. Hubert D, Dehillotte C, Munck A, David V, Baek J, Mely L, et al. Retrospective observational study of French patients with cystic fibrosis and a Gly551Asp-CFTR mutation after 1 and 2years of treatment with ivacaftor in a real-world setting. J Cyst Fibros. 2018; 17(1):89–95. [PubMed: 28711222]
26. Clinical and Functional Translation of CFTR Welcome to the CFTR2 website [Internet]Baltimore (MD): Johns Hopkins University; CFTR2; c2011 [cited 2018 Feb 26]. Available from: https://www.cftr2.org/mutations_history
27. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015; 16(1):45–56. [PubMed: 25404111]
28. Durmowicz AG, Lim R, Rogers H, Rosebraugh CJ, Chowdhury BA. The U.S. Food and Drug Administration's experience with ivacaftor in cystic fibrosis. Establishing efficacy using in vitro data in lieu of a clinical trial. Ann Am Thorac Soc. 2018; 15(1):1–2. [PubMed: 29020455]
29. Cystic Fibrosis FoundationFDA approves ivacaftor for 23 additional CFTR mutations [Internet]Bethesda (MD): The Foundation; 2017May 17. [cited 2018 Feb 26]. Available from: https://www.cff.org/News/News-Archive/2017/FDA-Approves-Ivacaftor-for-23-Additional-CFTR-Mutations/
30. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence—what is it and what can it tell us? N Engl J Med. 2016; 375(23):2293–7. [PubMed: 27959688]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

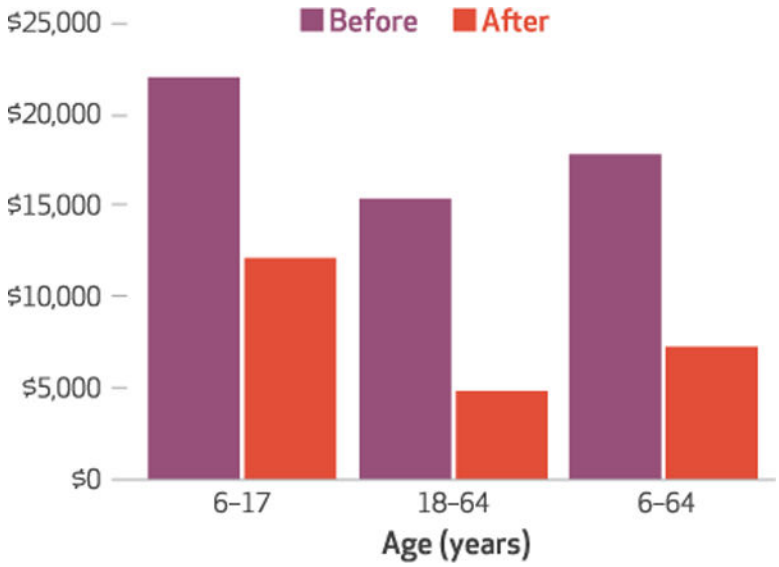

Exhibit 3. Mean inpatient spending during the twelve months before and twelve months after filling the first ivacaftor prescription, by age group, 2012–15

SOURCE Authors' analysis of data from the Truven Health Analytics MarketScan Commercial Research database. **NOTES** Patients' diagnosis codes, prescription fills, insurance coverage, and age are explained in the notes to exhibit 1. Inpatient admissions were for all causes. Total payments (allowable charges) on inpatient services during the twelve months before and the twelve months after filling the first ivacaftor prescription were calculated and adjusted to 2016 medical prices using the Personal Consumption Expenditures health price index of the Bureau of Economic Analysis, an unbiased measure of US medical inflation.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Exhibit 1

Inpatient admissions among patients with cystic fibrosis (CF) who filled a first prescription for ivacaftor, 2012–15

		Before filling prescription				After filling prescription					
		With at least 1 admission		Admissions		With at least 1 admission		Admissions		Decrease from before to after	
Age (years)	No.	No.	%	No.	Rate[a]	No.	%	No.	Rate[a]	% with admission	Rate[a]
ALL-CAUSE ADMISSIONS											
6-64	143	44	31	82	0.57	20	14	37	0.26	55	55
6-17	53	18	34	32	0.60	7	13	13	0.25	61	59
18-64	90	26	29	50	0.56	13	14	24	0.27	50	52
ADMISSIONS RELATED TO CYSTIC FIBROSIS											
6-64	143	23	16	42	0.29	5	4	8	0.06	78	81
6-17	53	10	19	17	0.32	2	4	3	0.06	80	82
18-64	90	13	14	25	0.28	3	3	5	0.06	77	80

SOURCE Authors' analysis of data from the Truven Health Analytics MarketScan Commercial Research database.

NOTES Patients had diagnosis codes indicating cystic fibrosis (see text for details). Patients also had at least one filled ivacaftor prescription during the period February 2012–December 2015 and were continuously enrolled in employer-sponsored health plans for at least twelve months before and twelve months after filling that prescription. Age was the age in years at the time of the first filled prescription. Inpatient admissions during the twelve months before and twelve months after filling the first prescription were calculated for all causes and for those with a cystic fibrosis–related diagnosis code. All changes in proportions were significant ($p < 0:01$) according to results from McNemar's one-tailed test of paired sample proportions using exact binomial probability calculations.

[a]Per person per year.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Exhibit 2

Inpatient admissions per twelve months for those filling a first prescription for ivacaftor, by number of prescription fills during the first 12 months of ivacaftor use, 2012–15

		Before filling prescription		After filling prescription		Decrease from before to after
Fills	Patients	Admissions	Rate[a]	Admissions	Rate[a]	
3–9	53	20	0.38	11	0.21	45%
10–12	90	28	0.31	9	0.10	68%

SOURCE Authors' analysis of data from the Truven Health Analytics MarketScan Commercial Research database.

NOTES Patients' diagnosis codes, prescription fills, insurance coverage, and age are explained in the notes to exhibit 1. Inpatient admissions were for all causes. Information about patients with 1–2 fills is not shown because of the small sample size.

[a]Per person per year.

Health Aff (Millwood). Author manuscript; available in PMC 2018 July 10.