Early View

Original research article

CFTR Modulator Use and Risk of Nontuberculous Mycobacteria Positivity in Cystic Fibrosis, 2011–2018

Emily E. Ricotta, D. Rebecca Prevots, Kenneth N. Olivier

Please cite this article as: Ricotta EE, Prevots DR, Olivier KN. CFTR Modulator Use and Risk of Nontuberculous Mycobacteria Positivity in Cystic Fibrosis, 2011–2018. *ERJ Open Res* 2022; in press (<https://doi.org/10.1183/23120541.00724-2021>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2022. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Title: CFTR Modulator Use and Risk of Nontuberculous Mycobacteria Positivity in Cystic Fibrosis, 2011-2018

Authors: Emily E. Ricotta, PhD, MSc^{1*}, D. Rebecca Prevots, PhD, MPH¹, Kenneth N. Olivier, MD, MPH²

1. Epidemiology and Population Studies Unit, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, Maryland, USA
2. Pulmonary Branch, National Heart, Lung, and Blood Institute, NIH, Bethesda, Maryland, USA

*Corresponding author

Emily Ricotta, PhD, MSc

Research Fellow

Epidemiology and Population Studies Unit

Division of Intramural Research

National Institute of Allergy and Infectious Diseases

National Institutes of Health

5601 Fishers Lane, 7D18

Rockville, Maryland 20852

Phone: 301-761-7784

Email: emily.ricotta@nih.gov

Summary: Therapeutic use of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, is significantly associated with a decreased risk of NTM positivity in individuals with cystic fibrosis.

Abstract

Background People with cystic fibrosis (CF) are at increased risk of pulmonary nontuberculous mycobacteria (NTM) disease. Cystic fibrosis transmembrane conductance regulator (CFTR) modulators are associated with reduced lung infection with pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This association has not been studied with NTM.

Methods Using encounter-level data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) from 2011-2018, we identified individuals >12 years old with ≥1 NTM-negative sputum culture and had information on receipt of ivacaftor therapy. We used a Cox proportional hazards model to assess the relationship between CFTR modulator usage (any and monotherapy vs combination therapy) and NTM sputum culture positivity, controlling for sex, least severe class of CFTR mutation, receipt of chronic macrolides, age, body mass index, and percent predicted forced expiratory volume.

Results Of 25,987 unique individuals, 17,403 individuals met inclusion criteria. During follow up, 42% of individuals received CFTR modulator therapy, and 23% had incident NTM. The median time to event was 6.1 years (IQR: 4.0 – 7.3 years) for those ever-receiving CFTR modulators compared to 4.0 years (IQR: 1.6 – 6.5 years) in those never receiving CFTR modulators. CFTR modulator use was associated with a significantly reduced hazard of NTM culture positivity (HR: 0.88, 95% CI: 0.79, 0.97); there was no significant difference in the hazard between those receiving ivacaftor monotherapy vs combination therapy (combination HR: 1.01, 95% CI: 0.79, 1.23).

Conclusions CFTR modulator therapy is associated with a decreased risk of NTM positivity in individuals with cystic fibrosis.

Background

Cystic fibrosis (CF) is a genetic disease defined by a progressive decrease in lung function which is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene[1]. The CFTR protein acts as a chloride channel whose normal function in the lung allows appropriate mucus development and clearance. When defects in CFTR are present this process cannot occur or is inefficient, leading to increased mucus in the lungs. CFTR mutations can result in reduced or no protein production, incorrect protein processing and trafficking, and/or insufficient gating and conduction [2]; there are over 1800 known deleterious CFTR mutations [3].

In 2009, a CFTR potentiator was identified that increased the channel opening probability in individuals with G551D class III gating mutations [4], and in 2012, the drug ivacaftor was approved by the US Food and Drug Administration for the treatment of individuals 6 years and older with the specific G551D mutation and in subsequent years for additional mutations such as R117H and for use in younger children. Monotherapy with ivacaftor has no effect in individuals with homozygous F508del CFTR mutations, the most common CFTR mutation (~70% of individuals), as class II mutations cause misfolding of the CFTR protein and therefore no trafficking of CFTR to the surface of the cell [5]. However, when ivacaftor is given in combination therapy with a CFTR corrector drug such as lumacaftor or tezacaftor that assists with protein folding and trafficking, improvement in lung function is observed [6, 7]. These drugs have collectively been referred to as CFTR modulators.

Because of decreased mucus clearing from the lungs and other host defense alterations of defective CFTR function, people with CF (pwCF) are at increased risk of acquiring acute and chronic lung infections with pathogens like *Pseudomonas aeruginosa*, *Staphylococcus aureus*,

and nontuberculous mycobacteria (NTM). Modulator therapy with ivacaftor has been associated with reduced lung infection with certain pathogens [8, 9], however this association has not been studied with NTM. The aim of this study was to assess the risk of developing an NTM positive culture in individuals receiving CFTR modulator therapy versus those not receiving modulators, controlling for specific CFTR mutations and mono- versus combination therapy.

Methods

Study population

We conducted a retrospective cohort study using encounter-level data from the US Cystic Fibrosis Foundation Patient Registry from 2011-2018. Individuals <12 years old, those who received a lung transplant, died, were positive for *Mycobacterium tuberculosis*, were never tested for NTM, only had one encounter, or had missing CFTR modulator treatment data for all years were excluded from analysis. Receipt of CFTR modulators between 2011-2018 was recorded, including whether individuals received ivacaftor monotherapy or combination therapy with lumacaftor or tezacaftor.

Survival analysis was conducted to assess the risk of NTM culture positivity comparing those who received CFTR modulator therapy to those who did not. A sub-analysis was done assessing NTM culture positivity risk by CFTR modulator type (ivacaftor monotherapy vs combination therapy with lumacaftor or tezacaftor), excluding individuals who had received both monotherapy and combination therapy (i.e. switched from one to the other). Species-specific analyses could not be run due to small numbers in most strata. The first negative NTM culture for an individual was used as the entry date for this study. Time to event was calculated as the number of days from a negative NTM culture to the first instance of a positive culture. CFTR

modulator treatment was included in the analysis as a time-varying covariate. Kaplan-Meier plots were created, and a Cox proportional-hazards model was used to assess the risk of having an NTM-positive lung culture using the “survival” package in R [10, 11]. Baseline covariates included in the model were an individual’s sex and their least severe CFTR mutation class (Class 1/2, Class 3, or Class 4/5). Encounter-level covariates included receipt of chronic macrolides, whether a mycobacterial culture was done, the number of sputum cultures an individual had up until that encounter, age (12- 17 vs ≥ 18 years old), body mass index (BMI), and percent predicted Global Lung Function Initiative (GLI) forced expiratory volume (FEV1%). The last non-missing observation for FEV1% was carried forward until the next non-missing value then categorized ($<40\%$ = “severe”, $\geq 40\%$ to $<70\%$ = “moderate”, $\geq 70\%$ $<90\%$ = “mild”, $\geq 90\%$ = “normal”) [12]. BMI was also carried forward and categorized, using BMI percentile for individuals aged 12-18 years (<5 = “underweight”, ≥ 5 to <85 = “normal”, ≥ 85 to <95 = “overweight”, ≥ 95 = “obese) and BMI value for individuals ≥ 18 (<18.5 = “underweight”, ≥ 18.5 to <25 = “normal”, ≥ 25 to <30 = “overweight”, ≥ 30 = “obese”). Logistic regression was used to assess the relationship between years of CFTR modulator usage and NTM positivity, controlling for sex, least severe mutation class, total number of sputum samples, end of follow-up age, FEV1%, BMI, number of sputum cultures, and years on chronic macrolides. Sensitivity analyses were conducted among people who had ≥ 3 positive NTM cultures (more likely to have NTM disease), people who provided at least one mycobacterial sample every other year (to control for detection bias), and without controlling for the cumulative number of sputum samples (in the event sputum samples acted as a mediator for NTM positivity).

Data analysis was conducted using R version 3.6.2 [13] The study was determined to be not human subjects research by the National Institutes of Health Office of Human Subjects Research Protection, and was approved by the CF Foundation Patient Registry Committee.

Results

From 2011 – 2018 there were 25,987 unique individuals ≥ 12 years old with encounters in the CFFPR; 17,403 individuals met inclusion criteria (Figure 1). This population was 52% male, and 67% received macrolides at least once during follow up; at the time of positive NTM culture or end of follow up, 79% were ≥ 18 years old, 54% of individuals were in the “normal” or “mild” FEV1% category, and 24% were overweight or obese. Class 1 mutations were found in 23% of individuals, class 2 in 86% (including 45% who were homozygous for the F508del mutation), class 3 in 5.8%, class 4 in 6.1%, and class 5 in 6.4% (Table 1). During follow up, 42% of individuals received modulator therapy (of these 7384 people, 26% received ivacaftor monotherapy during the study and 79% received combination therapy). Twenty-three percent of individuals had incident NTM (of these, 30% of positive cultures grew MAB only, 51% MAC only, 18% other only, 1.6% were mixed species). Median number of sputum samples was 3 for NTM positive individuals and 5 for NTM negative individuals. NTM was cultured from 10% of people who received CFTR modulator therapy and 33% of people who did not. Median follow up time was 5.0 years (IQR: 2.4 – 7.0 years) from the first negative culture.

Table 1. Individual and encounter-level characteristics at baseline and censoring time		
	Baseline N (%)	Censor** N (%)
Gender		
Male	9137 (52.5)	--
Female	8266 (47.5)	--
Mutation category*		

Class 1	4062 (23.3)	--
Class 2	15043 (86.4)	--
Class 3	1007 (5.8)	--
Class 4	1068 (6.1)	--
Class 5	1120 (6.4)	--
Unknown	668 (3.8)	
F508del only	7827 (45.0)	--
Least severe mutation		
Class 1/2	13614 (78.2)	--
Class 3	950 (5.5)	--
Class 4/5	2171 (12.5)	--
Unknown	668 (3.8)	--
Age		
12 to <18	6554 (37.7)	3694 (21.2)
≥18	10849 (62.3)	13709 (78.8)
FEV1pp		
Normal	3923 (22.5)	4313 (24.8)
Mild	4840 (27.8)	5125 (29.4)
Moderate	4959 (28.5)	5597 (32.2)
Severe	1210 (6.9)	2256 (13.0)
Unknown	2471 (14.2)	112 (0.6)
BMI		
Underweight	1135 (6.5)	1282 (7.4)
Normal	11517 (66.2)	10940 (62.9)
Overweight	2345 (13.5)	2852 (16.4)
Obese	839 (4.8)	1045 (6.0)
Unknown	1567 (9.0)	1284 (7.4)
Chronic Macrolides	7620 (43.8)	8192 (47.1)
NTM positive	--	4077 (23.4)
Culture positive for MAB only	--	1203 (6.9)
Culture positive for MAC only	--	2066 (11.9)
Culture positive for other species only	--	741 (4.3)
Culture positive for multiple species	--	67 (0.4)
Any modulator therapy	--	7384 (42.4)
Ever received Ivacaftor monotherapy	--	1893 (10.9)

Ever received combination therapy	--	5869 (33.7)
Neither		10019 (57.6)
*At least 1 **Censor = NTM positive culture or patient's last timepoint in dataset		

The Kaplan-Meier plot shows a higher probability of incident NTM for the group not receiving CFTR modulators compared to those receiving modulator therapy (Figure 2a). There was no difference in the probability of incident NTM between individuals receiving ivacaftor monotherapy vs combination therapy (Figure 2b). The median time to event was 6.1 years (IQR: 4.0 – 7.3 years) for those ever-receiving CFTR modulatory therapy compared to 4.0 years (IQR: 1.6 – 6.5 years) in those never receiving modulators. Using an adjusted Cox proportional hazards model, CFTR modulator therapy was associated with a significantly reduced hazard of NTM culture positivity (HR: 0.88, 95% CI: 0.79, 0.97). Receipt of combination modulator therapy compared to no therapy was associated with reduced hazard (HR: 0.88, 95% CI: 0.78, 0.98); monotherapy alone was not associated with decreased risk of NTM (HR: 0.89, 95% CI: 0.73, 1.08) nor was there a significant difference in the hazard between those receiving ivacaftor monotherapy vs combination therapy (combination HR: 0.99, 95% CI: 0.79, 1.23). Compared to those whose least severe mutation was Class 1/2, those whose least severe mutation was Class 4/5 had significantly increased risk of NTM (HR: 1.11, 95% CI: 1.01, 1.23), while those whose mutation class was unknown had a significantly reduced risk of NTM compared to individuals with Class 1/2 (HR: 0.79, 95% CI: 0.65, 0.97). The risk of NTM in Class 3 was not significantly different than Class 1/2 (HR: 0.96, 95% CI: 0.80, 1.15). For every additional year on CFTR modulator therapy, the odds of NTM positivity decreased by 37% (OR: 0.60, 95% CI: 0.58, 0.62), which is a larger effect size than the 16% decrease in the odds of NTM positivity for every

additional year on chronic macrolides (OR: 0.84, 95% CI: 0.82, 0.85). These results did not substantively differ in the sensitivity analyses (Supplemental table).

Discussion

Since the introduction of CFTR modulator therapy, there have been reports of decreased incidence of respiratory pathogens in pwCF who are on this treatment, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Aspergillus* spp. [8, 9]. However, trials assessing efficacy of CFTR modulators do not use acquisition of NTM, another important pathogen in the CF community, as an endpoint [14], even considering it exclusionary in some trials [15, 16]. This study presents the first evidence that CFTR modulator therapy reduces the risk of infection with pulmonary NTM (PNTM) using data from the CFFPR to assess the incidence and time to first NTM positive respiratory culture in individuals receiving modulator therapy compared to those who did not.

PwCF are at increased risk of developing PNTM due to their decreased ability to clear mycobacteria from the lungs, and NTM sputum positivity ranges from 14 – 19% across all ages in the US in 2019 [12, 17]. In this study, we found 23% of patients >12 years old had at least one NTM positive culture during the study period, which is in the range of prevalence estimates found among teens and adults with CF in the US previously [18, 19]. Because PNTM leads to progressive lung damage and decreasing pulmonary function, and increases the risk of death [20, 21], reducing the risk of NTM infection is of high priority. One of the frontline treatments for PNTM is macrolide therapy, which has been associated with improved outcomes in infected patients and reduced risk of infection the longer chronic macrolide therapy is received [18, 20]. However, macrolide resistance is an ever-present concern due to the use of chronic macrolide monotherapy for general disease management in pwCF and the possibility of acquired resistance

in NTM [21]. Therefore, prevention of infection with a therapy that is unlikely to result in drug-resistance would be ideal.

Because CFTR modulator use results in increased mucus clearance and pulmonary function, it seems logical that this therapy would reduce the risk of PNTM; indeed, our results support this hypothesis. Overall, fewer people ever receiving CFTR modulator therapy had an NTM positive sputum culture compared to those never receiving therapy (10% vs 33%), and time to culture positivity was significantly delayed among those receiving modulator therapy, a difference of 2.1-years. In adjusted analysis, the risk of having an NTM positive culture decreased by 14%, regardless of whether CFTR monotherapy or combination therapy was received. It is possible that no difference was observed between monotherapy and combination therapy because, while combination therapy has been observed to have a greater therapeutic effect than monotherapy in residual function CFTR heterozygotes [7], it may only take a mild improvement in CFTR function to decrease the risk of NTM culture positivity. Residual function (milder) genotypes were at increased risk of incident NTM in this study. Previous studies have shown that both NTM infections and milder CFTR genotypes were significantly more common in patients diagnosed with CF at a later age, likely due in part to greater longevity leading to longer NTM exposure time [18, 19].

One limitation of this study is that while a negative sputum culture was a requirement for inclusion in the analysis, we did not consider whether an individual had been NTM positive previously, nor did we look at whether ivacaftor is associated with the risk of recurrence or reinfection after the first positive culture. It is possible that because recurrence is at least partially related to structural risk factors like bronchiectasis, which itself is improved by restoration of CFTR function through modulator therapy, the risk of recurrence and reinfection would also be

decreased [22]. Another potential limitation is that we included anyone meeting the study criteria, regardless of their formal eligibility for receipt of CFTR modulator therapy; however, excluding individuals who are presently ineligible to receive any form of modulator therapy would likely strengthen the associations seen in this study.

Conclusions

CFTR modulator therapy is associated with decreased risk of and longer time to NTM culture positivity. It is possible that this decreased risk, along with that seen in other respiratory pathogens could result in reduced treatment burden in pwCF over time.

Acknowledgments

The authors thank the patients, care providers, and clinic coordinators at CF centers throughout the United States for their contributions to the Cystic Fibrosis Foundation Patient Registry

Funding

This research was supported by the Divisions of Intramural Research at the National Institute of Allergy and Infectious Diseases and the National Heart, Lung, and Blood Institute.

1. Riordan JR, Rommens JM, Kerem BS, Alon NOA, Rozmahel R, Grzelczak Z, Zielenski J, Lok SI, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collins FS, Tsui LC. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. *Science* American Association for the Advancement of Science; 1989; 245: 1066–1073.
2. Marson FAL, Bertuzzo CS, Ribeiro JD. Classification of CFTR mutation classes. *The Lancet Respiratory Medicine* 2016.
3. Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson JP, Urrutia A, Joubran J, Seepersaud S, Sussky K, Hoffman BJ, Van Goor F. Ivacaftor potentiation of multiple CFTR channels with gating mutations. *Journal of Cystic Fibrosis* Elsevier; 2012; 11: 237–245.
4. Van Goor F, Hadida S, Grootenhuys PDJ, Burton B, Cao D, Neuberger T, Turnbull A, Singh A, Joubran J, Hazlewood A, Zhou J, McCartney J, Arumugam V, Decker C, Yang J, Young C, Olson ER,

- Wine JJ, Frizzell RA, Ashlock M, Negulescu P. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proceedings of the National Academy of Sciences of the United States of America* National Academy of Sciences; 2009; 106: 18825–18830.
5. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordoñez CL, Geller DE. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* [Internet] Chest; 2012 [cited 2021 Nov 11]; 142: 718–724 Available from: <https://pubmed.ncbi.nlm.nih.gov/22383668/>.
 6. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, Lu Y, Lekstrom-Himes J, Elborn JS. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine* [Internet] Massachusetts Medical Society; 2017 [cited 2020 Feb 19]; 377: 2013–2023 Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1709846>.
 7. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine* [Internet] Massachusetts Medical Society; 2017 [cited 2020 Feb 19]; 377: 2024–2035 Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1709847>.
 8. Heltshe SL, Mayer-Hamblett N, Burns JL, Khan U, Baines A, Ramsey BW, Rowe SM. Pseudomonas aeruginosa in Cystic Fibrosis Patients With G551D-CFTR Treated With Ivacaftor. 2014 [cited 2020 Dec 29]; Available from: <https://academic.oup.com/cid/article/60/5/703/291737>.
 9. Frost FJ, Nazareth DS, Charman SC, Winstanley C, Walshaw MJ. Ivacaftor Is Associated with Reduced Lung Infection by Key Cystic Fibrosis Pathogens A Cohort Study Using National Registry Data. *Annals of the American Thoracic Society* 2019; 16: 1375–1382.
 10. Therneau T. A Package for Survival Analysis in R. 2020.
 11. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. New York, NY: Springer New York; 2000.
 12. Cystic Fibrosis Foundation. 2019 PATIENT REGISTRY ANNUAL DATA REPORT. .
 13. R Core Team. R: A language and environment for statistical computing. [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available from: <https://www.r-project.org/>.
 14. Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database of Systematic Reviews* John Wiley and Sons Ltd; 2019; .
 15. Davies JC, Moskowitz SM, Brown C, Horsley A, Mall MA, McKone EF, Plant BJ, Prais D, Ramsey BW, Taylor-Cousar JL, Tullis E, Uluer A, McKee CM, Robertson S, Shilling RA, Simard C, van Goor F, Waltz D, Xuan F, Young T, Rowe SM. VX-659–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine* [Internet] New England Journal of Medicine (NEJM/MMS); 2018 [cited 2021 Mar 21]; 379: 1599–1611 Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1807119>.

16. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, Ramsey BW, Rowe SM, Sass LA, Tullis E, McKee CM, Moskowitz SM, Robertson S, Savage J, Simard C, van Goor F, Waltz D, Xuan F, Young T, Taylor-Cousar JL. VX-445–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine* [Internet] New England Journal of Medicine (NEJM/MMS); 2018 [cited 2021 Mar 21]; 379: 1612–1620 Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1807120>.
17. Martiniano SL, Nick JA, Daley CL. Nontuberculous Mycobacterial Infections in Cystic Fibrosis. *Thoracic surgery clinics* [Internet] Elsevier Inc; 2019; 29: 95–108 Available from: <https://doi.org/10.1016/j.thorsurg.2018.09.008>.
18. Adjemian J, Olivier KN, Prevots DR. Epidemiology of Pulmonary Nontuberculous Mycobacterial Sputum Positivity in Patients with Cystic Fibrosis in the United Adjemian. *Ann Am Thorac Soc* [Internet] 2018 [cited 2021 Feb 18]; 15: 817–825 Available from: www.atsjournals.org.
19. Rodman DM, Polis JM, Heltshe SL, Sontag MK, Chacon C, Rodman R v., Brayshaw SJ, Huitt GA, Iseman MD, Saavedra MT, Taussig LM, Wagener JS, Accurso FJ, Nick JA. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* [Internet] American Thoracic Society; 2005 [cited 2021 Mar 24]; 171: 621–626 Available from: <http://www.atsjournals.org/doi/abs/10.1164/rccm.200403-404OC>.
20. Binder AM, Adjemian J, Olivier KN, Rebecca Prevots D. Epidemiology of Nontuberculous Mycobacterial infections and associated chronic Macrolide use among persons with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* [Internet] American Thoracic Society; 2013 [cited 2021 Mar 18]; 188: 807–812 Available from: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201307-1200OC>.
21. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, Noone PG, Bilton D, Corris P, Gibson RL, Hempstead SE, Koetz K, Sabadosa KA, Sermet-Gaudelus I, Smyth AR, van Ingen J, Wallace RJ, Winthrop KL, Marshall BC, Haworth CS. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax* [Internet] 2016 [cited 2021 Mar 24]; 71: i1–i22 Available from: https://thorax.bmj.com/content/thoraxjnl/71/Suppl_1/i1.full.pdf.
22. Sheikh SI, Long FR, McCoy KS, Johnson T, Ryan-Wenger NA, Hayes D. Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation. *Journal of Cystic Fibrosis* Elsevier; 2015; 14: 84–89.

Figure 1. Flowchart depicting inclusion criteria for CFTR modulator analysis from the Cystic Fibrosis Foundation Patient Registry, 2011-2018. This data included only individuals ≥ 12 years old.

Figure 2. Kaplan-Meier plots and 95% confidence intervals evaluating the event probability of patients having incident NTM cultures. A) Probability of incident NTM comparing receipt of any CFTR modulator therapy to non-receipt. B) Probability of incident NTM comparing receipt of ivacaftor monotherapy, combination therapy, or no modulator therapy.

	One or more positive NTM cultures			3 or more positive NTM cultures			Restricted to people with samples at least every other year			Not controlling for sputum		
	N events = 4077			N events = 1694			N events = 3032			N events = 4077		
	exp(coef)	lower .95	upper .95	exp(coef)	lower .95	upper .95	exp(coef)	lower .95	upper .95	exp(coef)	lower .95	upper .95
CFTR modulatory therapy	0.88	0.79	0.97	0.82	0.71	0.95	0.80	0.70	0.91	0.87	0.79	0.97
Combination vs no therapy	0.88	0.78	0.99	0.90	0.77	1.05	0.83	0.72	0.97	0.87	0.78	0.98
Monotherapy vs no therapy	0.89	0.73	1.08	0.62	0.47	0.82	0.72	0.57	0.91	0.88	0.73	1.07
Combination vs monotherapy	0.99	0.79	1.23	1.45	1.07	1.98	1.16	0.88	1.52	0.99	0.79	1.23
Class 3 vs Class 1/2	0.97	0.83	1.12	1.05	0.82	1.34	1.16	0.97	1.39	0.94	0.81	1.09
Class 4/5 vs Class 1/2	1.12	1.01	1.23	1.23	1.06	1.43	1.12	1.00	1.25	1.11	1.01	1.23
Unknown mutation class vs Class 1/2	0.79	0.65	0.97	0.70	0.49	1.00	0.79	0.63	0.99	0.78	0.63	0.95