Minority patients miss out on cystic fibrosis drugs due to genetic test limitations

3 February 2021

Credit: CC0 Public Domain

There is an impassioned debate taking place in medicine on whether race-based considerations should be a factor in research, diagnoses, or treatments. Those on one side assert that race should be ignored entirely because it is a societal construct with no biological basis, and accordingly many hospitals are abandoning long-established 'race corrections' in medical algorithms and diagnostics. Others, like Meghan McGarry, MD, MS, assistant professor of pediatrics at UC San Francisco, say that we can't completely ignore race, precisely because science is rarely free of societal influence—the structural inequality of our institutions affects the investments we make in research, drug development, and care.

In a paper published Feb. 1, 2021 in *Pediatric Pulmonology,* McGarry and co-author Susanna A. McColley, MD, of Northwestern University's Feinberg School of Medicine, show how non-white patients are effectively disqualified from receiving the latest precision medicines to treat cystic fibrosis (CF). These drugs were approved by the U.S. Food and Drug Administration (FDA) for people with specific mutations, but non-white patients are more likely to carry different CF mutations. Because these other mutations aren't included in genetic tests to qualify for the drugs, doctors cannot prescribe these new treatments for non-white patients, and insurance carriers won't cover the cost.

"The new drugs are remarkable—they take people from almost needing a lung transplant to leaving the hospital within days," said McGarry. "The problem is that these drugs are only approved for people with specific mutations, and everyone else gets left out. That is going to increase preexisting disparities."

CF is a rare but devastating disease caused by genetic mutations in a single gene, called CFTR. This gene codes for a pore, or channel, in cell membranes that allows water and chloride ions to enter and exit cells. Mutations in the CFTR gene can compromise the function of these channel proteins, leading to thickening of mucus and ensuing infections in the lungs and intestines of affected individuals.

Decades ago, most CF sufferers died by the age of five, but thanks to medical advances, including recently approved drugs known as CFTR modulators—which improve the function of the faulty channel proteins that result from CFTR gene mutations—the average life expectancy in CF today is 44 years.

McGarry first encountered the genetic differences between white and non-white CF patients in 2019 while working on a study in Puerto Rico with Esteban Burchard, MD, MPH, a pulmonologist and professor of bioengineering and therapeutic sciences at UCSF. They were investigating why 25% of Puerto Rican CF patients consistently test negative on standard CF screenings. After sequencing the genomes of 21 Puerto Rican and 61 Dominican CF patients they found that the most common CF mutations recognized in the United States were quite rare in these populations,

findings which suggested that there was a limited understanding in the medical community of the range of possible CFTR mutations.

The new study confirms and expands upon these findings. Using the Cystic Fibrosis Foundation's patient registry, which catalogs all the CF patients in the United States, McGarry and McColley analyzed how many patients had genetic mutations that confer eligibility for CFTR modulator drugs based on their U.S. Census-defined racial group. They found wide disparities in eligibility for the various groups, with about 94% of non-Hispanic white patients eligible for the drugs, but only about 75% of Hispanic patients and 70% of Black patients meeting current screening guidelines.

These numbers are not surprising considering that the clinical trials for CF modulators included almost exclusively non-Hispanic white participants. For example, in clinical trials for the drugs elexacaftor, tezacaftor and ivacaftor, the number of Black, Hispanic and Asian patients combined made up only around 5% of total trial participants.

"Drug companies sought approval for these drugs based solely on the most common CF mutations overall, because the bulk of CF patients are non-Hispanic white," said McGarry. "But that's not how we should be allocating drugs for rare, life-threatening diseases in children."

McGarry and McColley also analyzed a measurement of lung function used to assess symptoms in CF patients called forced expiratory volume, or FEV1. They found that patients who took CFTR modulators had better FEV1 results regardless of their specific mutation. In a previous study, McGarry demonstrated that even patients without any of the required CF mutations still experienced improved pulmonary benefits from CFTR modulators, demonstrating that these drugs can benefit many more patients than just those with mutations approved by the FDA.

"This is a cautionary tale of how not to do precision medicine," said McGarry. "Right now, we're widening disparities and we don't have a path to correct it."

McGarry contends that the way in which clinical trials recruit participants is a form of structural racism. Researchers often seek out trial participants locally, which is a problem if the community is majority non-Hispanic white. If researchers do want more diverse participants, they often need to pay for translation, transportation costs, and lost wages. McGarry said that researchers should be including these costs in their grant applications and thinking more broadly about diversity in all aspects of their work.

"If you want to have minorities in your study, your research team should not be all non-Hispanic white," said McGarry.

More information: Meghan E. McGarry et al, Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype, *Pediatric Pulmonology* (2021). DOI: 10.1002/ppul.25285

Provided by University of California, San Francisco