Medical News & Perspectives

Tackling the Misconception That Cystic Fibrosis Is a "White People's Disease"

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Neither Terry Wright nor his wife, Michele Wright, PhD, will forget the day 20 years ago when a physician told him, "If you weren't African American, I'd say you have the classic symptoms of cystic fibrosis [CF]."

So, his wife recalled in an interview, "We crossed it off the list" and continued seeking explanations for Wright's lifelong gastrointestinal and respiratory problems.

"Terry has been hospitalized more times than we've been on dates," she noted.

Because he doesn't fit the stereotype of what someone with CF looks like—in other words, he doesn't look like a White person of Northern European descent—Wright wasn't diagnosed until he was 54 years old. That's about 8 years older than the average life expectancy of neonates born with CF in 2017, the year that Terry finally uncovered the root cause of his health issues.

"That biased thinking caused him years of suffering and almost cost him his life several times over," his wife said.

"No Excuse"

Wright might be an outlier, but the notion that members of racial or ethnic minority groups couldn't possibly have CF has regularly resulted in delayed diagnoses and treatment. That's one reason why, according to the Cystic Fibrosis Foundation (CFF), Black and Hispanic people with CF are nearly twice as likely to die before their 18th birthday as White people with CF.

"It is racism, because it is assuming something about somebody based on their race," Susanna McColley, MD, associate director of the Cystic Fibrosis Center at Ann & Robert H. Lurie Children's Hospital at Northwestern University, said in an interview. "You can say it's misdiagnosis or lack of knowledge, but there is no excuse for looking at someone who has symptoms and not thinking about what it could be and thoroughly evaluating all of those things."

Not only are underrepresented minority patients with CF less likely to be properly diagnosed than White patients, but their symptoms are more likely to be attributed to their behavior, McColley said. For example, she said, clinicians might blame chronic pancreatitis, a common CF symptom, on alcohol use disorder in racial or ethnic minority patients. And, McColley said, if a child is malnourished and fails to thrive, physicians might suspect abuse and contact social services instead of considering that the findings could be CF-related gastrointestinal problems.

Michele Wright, PhD/National Organization of African Americans with Cystic Fibrosis

"I think because the vast majority of people with cystic fibrosis are White…for many physicians, the assumption was only people who are White get this disease," Michael Boyle, MD, the CFF's president and chief executive officer, said in an interview.

Of the 31 199 patients in the CFF's registry in 2019—the most recent year for which data are available—4.7% identified as Black individuals, 3.8% identified as neither White nor Black individuals, and, among people of all races, 9.4% identified as Hispanic.

The CFF acknowledged in November 2020 that recognition of Black individuals and people of other racial and ethnic backgrounds within the CF community has been inadequate. As they asked for input from these communities to help address racism and discrimination, CFF leaders said preliminary talks with health disparities researchers and underrepresented minority patients with CF and their families, including the Wrights, led to critical insights.

"In those conversations, sobering evidence affirms that race impacts every aspect of an individual's experience with CF," according to a statement from the foundation, which only recently began including members of racial and ethnic minorities among the photos of patients and families on its website.

Missed at Birth

One might wonder how CF cases could go undiagnosed, given that all 50 states and the District of Columbia have mandated newborn screening for the disease since 2010, and many required it for years before then.

But, McColley said, "We have seen kids who were completely missed by newborn screening. We can't know exactly how many are missed."

Newborn screening checks to see if infants have elevated levels of immunoreactive trypsinogen (IRT), a pancreatic enzyme precursor. Elevated IRT can be a sign of CF, but it also can be associated with other factors, such as a premature or stressful delivery.

In many states, the next step in screening newborns with elevated IRT is DNA testing to check for a minimum of 23 common variations in the CF transmembrane conductance regulator (*CFTR*) gene that cause CF. People with CF inherited a disease-causing *CFTR* variation from both of their parents. CF carriers inherited a *CFTR* variant from only 1 parent.

If screening suggests CF, infants are referred for a sweat chloride test for confirmation. Infants who have CF detected by newborn screening usually are diagnosed at 2 weeks to 4 weeks of age.

But Asian, Black, and Hispanic infants are less likely to have those common CF-causing *CFTR* variations, so their elevated IRT levels are more likely to be attributed to something other than CF, delaying their diagnosis until symptoms appear. Or maybe not even then, as was Wright's experience.

Delayed CF diagnosis can have long-lasting adverse effects.

"We do newborn screening because it's very clear that you can have malnutrition within the first few weeks of life" with undiagnosed CF, McColley explained. But if CF is detected shortly after birth and treatment started immediately, she said, "It improves your nutrition up into the teenage years, and your nutritional status is a major marker of mortality."

The Elephant in the Room

For years, Wright had "really bad" sinusitis. His abdomen hurt incessantly. He couldn't keep food down. All are CF symptoms, but his encounters with physicians over the years played out like the parable from India, "The Blind Men and the Elephant."

Like the men in the parable, who envisioned only the individual parts of the elephant, rather than the sum of those parts, the physicians Wright encountered over the years diagnosed him with pancreatitis, asthma, and ulcers but failed to recognize that CF tied all his symptoms together. When he told physicians that his skin was salty and he was constantly dehydrated, they recommended taking electrolytes instead of ordering a sweat chloride test.

"They started calling all these organs out without doing a proper diagnosis," recalled Wright, a personal trainer and master gardener who, despite his CF, has completed marathons and 100-mile bicycle rides.

Finally, the Wrights, who live in North Little Rock, Arkansas, had had enough. Terry had spent a month in the hospital in late 2016 and another month in early 2017 for treatment of infections caused by aspergillus, a species of fungus, and *Staphylococcus aureus*, both of which are common in the airways of people with CF.

His wife, an engineer with a PhD in public policy who at one time worked as a pharmaceutical salesperson, asked that an infectious disease specialist be brought in but was told her husband wasn't sick enough. Frustrated, she took matters into her own hands and scheduled an appointment with a pulmonologist in the University of Arkansas for Medical Sciences (UAMS) infectious disease division.

Within a half hour of meeting Wright, the UAMS physician concluded that he most likely had CF and referred him for a sweat chloride test, which confirmed that Wright had the genetic disorder that another physician dismissed more than 15 years earlier.

Complicating matters, after Wright was finally diagnosed, genotyping revealed that he, like about 30% of Black patients with CF, had rare *CFTR* variations and was ineligible for treatment with CFTR modulators, the only drugs that target the underlying cause of CF. More than 90% of White patients are eligible for the modulators, designed to correct the malfunctioning protein made by the *CFTR* gene, which normally helps maintain the balance of sodium and water on body surfaces, including the lungs' surface.

A few months after his diagnosis in 2017, Terry was hospitalized yet again. Word of "this old Black man with cystic fibrosis" quickly spread through the hospital, he recalled, sending a stream of hospital staff to his room to see for themselves.

The Wrights don't want anyone else with CF to struggle as much as they did for an accurate diagnosis. Toward that goal, they founded the National Organization of African Americans with Cystic Fibrosis. Wright wrote about his rocky path to a diagnosis for the latest edition of Patient Voices, published by the American Thoracic Society (ATS) and also penned a children's book about it, *Terry's Journey to CF Land*.

And, with the help of Jennifer Taylor-Cousar, MD, codirector of the Adult Cystic Fibrosis Program at National Jewish Health in Denver, the Wrights developed a CF screening tool for individuals who think they might have the disease—especially those who are Black, Asian, Indigenous, or Hispanic—and their physicians.

"Regardless of your race and ethnicity, you should ask your doctor about the possibility of undergoing a sweat test and a genetic test for CF," the screening tool advises people who have a combination of 8 signs and symptoms, most of which Wright experienced for years before being diagnosed.

"White People's Disease"

Taylor-Cousar had planned to specialize in neonatology. But at Duke University, where she attended medical school and completed her residency in internal medicine and fellowships in pulmonary disease, pediatric pulmonology, and pulmonary disease and critical care medicine, she became intrigued with CF because it involved respiratory problems as well as chronic infections, both of which interested her.

Although she saw Black patients with CF at Duke, she got pushback from her fellow Black trainees when she decided to pursue a career studying and treating the disease. "Why do you want to go into this? It's a White people's disease," she recalled some telling her.

Taylor-Cousar is quick to point out that the first physician to describe CF noted that some patients were members of racial or ethnic minorities. On the first page of a 1938 article, published in the forerunner of *JAMA Pediatrics*, Columbia University pathologist Dorothy Andersen, MD, wrote that among the patients in her case series of 49, 1 was a Black child, and others were born to parents from Puerto Rico.

In part, Taylor-Cousar credits the Black Lives Matter movement and the COVID-19 pandemic for increased attention paid to racial disparities in health care in general and CF specifically. But still, the "White people's disease" notion persists, she said, recalling a recent conference on difficult pulmonary cases at which a presenter discussed a patient with classic CF symptoms. One attendee, Taylor-Cousar recollected, interjected, "Oh, but he's Black," so he couldn't have CF.

"Cystic fibrosis can occur in somebody of any race, and by not diagnosing people when you should, you're making their prognosis much poorer than it needs to be, and you may be excluding them from getting drugs that could completely change their lives," Taylor-Cousar said.

Shut Out

CFTR modulators have transformed management of CF. Four such drugs have been approved by the US Food and Drug Administration; all are marketed by Boston-based Vertex Pharmaceuticals.

The first CFTR modulator, ivacaftor (Kalydeco), was approved in 2012 for treating people with CF who had at least 1 copy of a specific *CFTR* variant. At the time, Vertex estimated that about 1200 US individuals with CF, or about 4% of that population, would be eligible for ivacaftor.

Today, about 90% of people with CF in the US have genetic variants eligible for treatment with at least 1 of the CFTR modulators, each of which is indicated for scores of variants. That 90% "sounds like a great number," Megan McGarry, MD, said in an interview. However, she said, "That's not the way it is uniformly. We have a lot of work to do for certain groups."

In a recent cross-sectional study of 30 775 patients in the 2018 CF Foundation

Patient Registry, McGarry, a pediatric pulmonologist at the University of California, San Francisco, and McColley found that for each CFTR modulator, Black patients were least likely to have eligible variants while non-Hispanic White patients were most likely.

Overall, 92.4% of non-Hispanic White patients had variants eligible for a CFTR modulator, compared with 69.7% of Black patients, 75.6% of Hispanic patients, and 80.5% of other racial categories. And across the board, the lowest pulmonary function was seen in patients ineligible for the drugs.

Breathing New Life

McGarry told of a 12-year-old Hispanic child with CF who was on the verge of needing a lung transplant. Since she was diagnosed, she'd been hospitalized 19 times. She couldn't go to school, she couldn't sleep, and she couldn't walk more than a block.

At the time, ivacaftor had just received FDA approval, but it was indicated only for patients with 1 of 10 known "gating" variants. While the initial gating variant eligible for ivacaftor occurs in 4% of patients with CF, the remaining 9 variants occur in a total of 1%.

The CFTR protein is like a tunnel with a gate. Normally, cells open the gate when necessary to allow chloride to pass through, and then they close it. But gating variants lock the gate closed, blocking the passage of chloride.

The young Hispanic patient had 1 of the rare gating variants. In vitro, ivacaftor improved chloride transport in all 10 gating variants, and McGarry's mentor suggested giving the drug to the patient despite the rare variant.

Most families can't afford to pay out-of-pocket for CFTR modulators—the list price for ivacaftor is more than $300 000 per year—but the girl had public insurance that covered off-label use of ivacaftor. "We had a private donor who then donated money so we could get the drug for a bunch of other patients," McGarry added.

The modulator worked even better for the patient with the rare variant, who is now a young adult, than it did for some patients with the gating variant indicated on the label, McGarry said. The girl's sweat chloride level normalized within 2 weeks of starting treatment, her cough cleared completely in 3 weeks, and she was able to participate in physical education classes at school 4 weeks later.

"We went to the insurance company and showed them a cost-benefit analysis. We published it right away," McGarry recalled. "Other doctors did the same thing with insurance companies to get it for their patients."

Theratyping 1 Patient at a Time

Each of more than 1000 rare *CFTR* variants is found in only 5 or fewer patients with CF worldwide, said Boyle, who, before joining the CFF, founded and directed the Johns Hopkins University Adult CF Program, where he still sees patients. "From the beginning, we knew there were going to be challenges in trying to do clinical trials of those because of their small numbers," he said.

Instead, the CFF research laboratory and other centers are "theratyping" patients to see if they might benefit from CFTR modulators that aren't yet indicated for their rare variants. A trained professional rubs a small brush in patients' nostrils to collect epithelial cells. The cells are cultured in the lab with approved CFTR modulators, and researchers look for biomarkers that show the cells are responding.

By the end of 2020, epithelial cells from 44 out of 96 patients sampled responded to a CFTR modulator at Cincinnati Children's Hospital, pediatric pulmonologist John Brewington, MD, said in an interview.

"The purpose of the study is to understand if these nasal cell–based models can predict what will happen when someone starts therapy in these rare variant groups," Brewington said. "The overall big-picture goal here is to figure out how we can use the lab to inform an individual person's care." The results have not yet been published, but, he said, "in broad strokes, the model definitely predicts what happens."

With permission, Brewington's lab shares findings with patients' physicians. About three-fourths of the 44 patients whose cells responded to a CFTR modulator have started taking the drug, Brewington said. "We often get pulled into the conversation about insurance coverage," he added.

Brewington said his lab has not been collecting information about the race and ethnicity of patients who submit nasal epithelial cells for evaluation. "That's a huge oversight on our part," he acknowledged, adding that he plans to rectify it.

Vertex uses a different, more easily replicated approach to theratyping. Instead of testing CFTR modulators against individual patients' cells, the company's in vitro assay uses Fischer rat thyroid cells that express rare variants. "We have established a novel regulatory pathway to use our cell model-based data to predict responsiveness," Vertex spokeswoman Heather Nichols said in an email.

The FDA based its 2014 decision to expand ivacaftor eligibility to all 10 gating variants on clinical trial data. But in 2017, the agency began basing expanded indications for CFTR modulators on data from Vertex's Fischer rat thyroid cell in vitro assay instead of on clinical trials.

The CFF estimates that about 7% of patients have rare variants that don't produce any CFTR protein, so they have nothing for a modulator to correct. In 2019, the CFF launched its "Path to a Cure," a $500 million research agenda to accelerate treatments for every person with CF, regardless of their variants.

Feeling Good

On December 21, 2020, the FDA expanded eligibility for 3 CFTR modulators, adding scores of rare variants for each. Vertex estimated that a total of 600 US patients could benefit from the expansion.

Wright was 1 of them.

He began taking Trikafta, a combination of 3 CFTR modulators (elexacaftor, tezacaftor, and ivacaftor) about a month after the FDA expanded the medication's indications, adding 177 rare variants to its label. The FDA originally approved the drug in late 2019 for patients who had at least 1 copy of the most common CFTR variant, found in about 90% of patients but not in Wright.

About 2½ months after he began taking the drug, Wright no longer had sinus congestion. His appetite returned as his gastrointestinal problems subsided, and he'd gained 20 pounds. "My energy level is much better," he said. "It's just remarkable." ■

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