Redefining a disease

A proposal to expand the diagnostic criteria for chronic obstructive pulmonary disease puts overlooked groups of patients in the spotlight. **By Amanda Keener**

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Spirometers can be used to measure lung function, but results often indicate that people with the symptoms of COPD are healthy.

Pulmonologist James Crapo might be semi-retired, but that hasn't stopped him from trying to revolutionize the field of chronic obstructive pulmonary disease (COPD). At 76, Crapo remains co-director of a massive observational study of smokers across the United States called COPDGene, which he and his colleagues started 12 years ago at National Jewish Health in Denver, Colorado. Since 2008, COPDGene researchers have worked to define the spectrum of disease courses that lead to COPD by tracking the health and genetics of more than 10,000 current and former smokers. The researchers' main goal is to understand why only some people develop the disease. But along the way, the data have led them to conclude that the current definition of the disease is much too narrow. As far as Crapo is concerned, it needs to be completely rewritten.

Since the late 1990s, COPD has been diagnosed according to a set of criteria developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Clinicians base their diagnoses on a person's symptoms – a persistent cough, heavy mucus production and shortness of breath – as well as their exposure to risk factors such as smoking and the results of a test of lung function, called spirometry, that measures how much air a person can force out. The lung-function score must be below a certain threshold for a person to be diagnosed with COPD.

The difficulty is that there are huge numbers of people who have the symptoms of COPD, and clear signs of airway inflammation and lung damage on computed tomography (CT) imaging, but whose lung-function tests indicate that they are healthy. Within the COPDGene cohort, nearly 40% of the people who didn't meet the definition of COPD when they joined the study had late-stage disease five years later[1].

"Many smokers are symptomatic despite a normal lung function – they should not be considered healthy," says Frits Franssen, a respiratory physician and researcher at the Maastricht University Medical Center in the Netherlands. "We all know that there are patients that have rather severe emphysema but normal spirometry, and it's a challenge to classify these patients." Without a formal diagnosis of COPD, these people are left out of clinical trials. Clinicians don't have the evidence they need to tell such patients what to expect and to choose the best treatments. Physicians usually treat the symptoms, often with the same drugs used for COPD, but without knowing what biological process they are targeting or whether the drugs will have long-term benefits.

Crapo thinks that the best way to ensure these patients are diagnosed and can take part in clinical trials is to introduce new subtypes of COPD. That requires new diagnostic criteria. In November 2019, he and around 100 other researchers proposed a revised system for COPD diagnosis that takes into account lung inflammation and tissue damage captured with CT imaging, and uses a broader definition of abnormal lung function, in addition to existing criteria of a history of smoking and displaying symptoms of the disease[2]. The expanded criteria would increase the number of people in the United States diagnosed with COPD by 5–10 million, Crapo says.

Without evidence on how best to treat these patients, it is unlikely that GOLD will adopt the new criteria in full, says Meilan Han, a pulmonologist and researcher at the University of Michigan in Ann Arbor who is both a COPDGene investigator and a member of GOLD's scientific committee. Still, most COPD researchers are coming around to the idea that there is a group of people that research has long overlooked. "We have these symptomatic patients with a real problem that has no name, whether they have COPD or not," Han says.

The GOLD standard

COPD was first defined in the late 1950s, but it was largely neglected by researchers until the 1990s. The attitude towards patients was, "just stop smoking", Crapo says. The only available drugs were borrowed from asthma. So in 1997, a group of pulmonology researchers, as well as representatives from the World Health Organization and the US National Heart, Lung, and Blood Institute, formed GOLD as a way to raise awareness of COPD, standardize its diagnosis and encourage research on prevention and treatment.

Spirometers were already used at the time for conditions such as asthma, and they became the tool of choice to determine whether a person's breathing was obstructed. A spirometer is essentially a set of tubes attached to sensors that measure airflow. To test for COPD, a person is told to fill their lungs and forcefully breathe into the spirometer, which measures the amount of air that is pushed out.

To determine whether a person's airways are obstructed, clinicians compare the amount of air the patient can blow out in one second, called the forced expiratory volume (FEV1), to the total volume of air that they can exhale, known as forced vital capacity (FVC). According to GOLD, a person can be diagnosed with COPD if the ratio of FEV1 to FVC is below 0.7 — meaning the person exhales less than 70% of the air in their lungs in one second.

The American College of Physicians, the US Food and Drug Administration and the European Medicines Agency have all adopted the GOLD criteria. But Crapo calls them "the golden handcuffs", because the strict cut-off for diagnosis excludes two populations of patients.

First, there are those who experience episodes of intense symptoms called exacerbations, but pass the spirometry test with flying colours. Han is leading a project, called the subpopulations and intermediate outcome measures in COPD study, which has found that this group of people have airway thickening on CT scans and that their symptoms are similar to those seen in people with first- or second-stage COPD[3].

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The second group left out also has symptoms, exacerbations and a low FEV1, but, for whatever reason, the total lung volume of people in this group is also low, putting their spirometry ratio above 0.7. This is referred to as preserved ratio impaired spirometry, or PRISm. Those affected are prone to symptoms such as breathlessness and coughing that can interfere with normal physical activity such as walking. They also have a higher risk of death compared with people with normal FEV1 values. People can have PRISm for a variety of reasons, but for a long time it was assumed that most had fibrotic lung disease.

The COPDGene study excluded individuals with any fibrotic lung disease. This allowed researchers to conduct a long-term, detailed comparison of the health of smokers who fell into the PRISm group with those who met the GOLD criteria or had normal spirometry. Participants had clinical examinations, spirometry tests, CT scans of their lungs and blood tests at an initial assessment and then again five years later. The goal was to find genes or clinical features that could help to predict which smokers would develop COPD and how fast it would progress.

It turned out that current spirometry-based measures used for diagnosis were not the strongest predictors of worsening disease and death, says John Hokanson, who is head of epidemiology for COPDGene, and based at the Colorado School of Public Health in Aurora. His team's analysis revealed that CT evidence of emphysema (a condition in which the air sacs of the lungs are damaged) and inflammation in the airways were the best predictors of disease progression and mortality[4]. The more extensive the airway inflammation, emphysema or both, the more likely it was that the person's disease would progress or that they would die, regardless of spirometry values.

People with signs of emphysema tended to follow the classic trajectory of COPD: first developing a low spirometry ratio but with normal FEV1, then moving on to full-blown disease. People with CT evidence of airway inflammation, however, had a completely different disease course. Half of them already had COPD, as defined by GOLD. The other half started with PRISm and, after five years, nearly 30% had developed stage 2, 3 or 4 COPD — skipping the earliest stage that would be identified by spirometry. Importantly, the PRISm in these people was not the result of fibrosis or some other condition — an indication that the disease process that led to COPD was underway years before they received an official diagnosis.

When he first saw the data, Crapo told the epidemiology team, "Oh my gosh, you just changed the diagnosis of COPD." The researchers had revealed a substantial group of people who don't meet the current COPD definition, but are nonetheless at high risk of dying from the disease. He thinks that these people should be identified and treated as early as possible — and that the best way to do that is to create several categories of COPD defined by a combination of symptoms, CT imaging, exposure to risk factors, and a low FEV1 or FEV1:FVC ratio.

Mixed reactions

Crapo is not alone in thinking that COPD diagnosis needs a revamp. "I had no trouble finding 100 other authors to put on the paper," he says. But there are doubts about whether the COPDGene proposal is the best way forward.

Even some co-authors of the proposal stress that it needs refinement. "I don't think that our proposed diagnostic criteria is the ultimate best classification," says Edwin Silverman, a pulmonologist at Brigham and Women's Hospital in Boston, Massachusetts, and COPDGene co-director. As the COPDGene team learns more about the biology behind the patterns they're seeing, he says, its scheme will be updated.

Han says she's not convinced that the airway inflammation and emphysema pathways will encompass all people with COPD. The relationship between each pathway and mortality risk is statistically complex and is based on data from people in the United States aged 45 or older who smoked heavily — at least one pack of cigarettes per day — for at least a decade

outlook

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Meilan Han (right) is investigating the different forms of chronic obstructive pulmonary disease.

and often much longer. It's unclear whether Crapo's proposed criteria would work well in other groups, including the 10–20% of people with COPD who have never smoked.

On this point, Crapo and Hokanson are encouraged by data from other long-term population studies that have included non-smokers. An analysis of a population study that included nearly 5,500 smokers and non-smokers aged 45 and over in the Netherlands showed that half of people with PRISm progressed to COPD within four-and-a-half years[5]. "With respect to PRISm, we entirely replicate [the COPDGene] findings," says lead author Guy Brusselle, a respiratory physician at Ghent University Hospital in Belgium. His team is now analysing CT images from a subset of the participants of the Dutch study to see whether it can also replicate COPDGene's findings on the airway inflammation and emphysema disease pathways.

Meanwhile, Hokanson's team is analysing the third wave of COPDGene cohort data, and is finding that ten years after the start of the study, airway inflammation and emphysema are still strong predictors of disease progression and mortality. The team has also found that two genetic signatures linked to COPD align neatly with the two disease pathways. For Hokanson, that is strong evidence that these are real biological processes that lead to COPD, but he acknowledges that there are still a lot of gaps to fill.

Some critics argue that COPDGene's proposal is just not practical. Franssen says that the reliance on CT imaging makes it infeasible outside high-income countries. "It really conflicts with the basic idea of GOLD, that it should be simple and applicable all over the world," he says. However, others argue that CT imaging is becoming more widespread, especially as part of lung-cancer screening programmes.

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Brusselle sees considerable benefits to drug development that could come from expanding the technology's use in diagnosis. Just sorting people into two general groups of airway-inflammation-dominant or emphysema-dominant COPD would mean more-focused clinical trials, which are much needed in a field plagued by failure. As a clinician, however, he doesn't think that the COPDGene scheme offers much for patient care. It's based on statistical risk, and includes eight classifications such as possible or probable COPD. "You can't tell a patient, 'you have probable COPD'," Brusselle says. "We need other terms."

Evidence gap

Crapo had planned to argue for revising the diagnostic criteria at a meeting of the American Thoracic Society in May. However, the meeting was cancelled as a result of the COVID-19 pandemic, and it is currently unclear when issues such as these will be discussed.

Han has already briefed the GOLD scientific committee on the COPDGene data at the European Respiratory Society meeting last September, and she suspects that it will look for formal ways to define the groups of patients who don't meet the spirometry criteria but who are at risk of COPD or have COPD-like symptoms.

David Halpin, a consultant physician at the Royal Devon and Exeter Hospital, UK, who serves on GOLD's scientific committee and board of directors, says he doesn't think there are enough data about these patients to assign formal diagnoses – especially because GOLD can't make evidence-based-treatment recommendations for them. "We'd like to know how best to treat them, but without any evidence we can't make recommendations," he says.

Han says this puts GOLD in a catch-22 situation: the organization can't recommend treatments for these patients without clinical trial evidence, but without names for these conditions there are no regulatory frameworks for such trials to take place, and drug companies are hesitant to enter the space. To help fill the evidence gap, Han and her colleagues are recruiting symptomatic patients with normal spirometry results to test whether a combination of two bronchodilators – medication that relaxes lung muscle and widens the airways – reduces their symptoms and improves their quality of life. There are no drug trials in the works for people with PRISm.

Crapo says that people with PRISm in the COPDGene cohort who happen to be receiving treatment tend to score higher on quality-of-life scales, but the numbers are small and the study is not designed to test interventions. He hopes that his proposal will encourage pharmaceutical companies to start studying these patients more systematically, and has been meeting with industry researchers to offer advice on designing such trials.

Crapo knows it's unlikely that GOLD will change the diagnostic criteria for COPD immediately, if at all. And he is aware that the proposed criteria need refinement and further study. But he firmly believes that waiting for lung function to decline before making a diagnosis is waiting too long. "Every single PRISm patient has high risk for progression and mortality," he says. "That's got to be recognized."

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