Taking Precise Aim at Lung Disease

What is "precision medicine"? Despite that the concept is more than a century old and the term was officially coined in 2011 (1), this buzzword has gone "viral" in recent years, propelled by rapid emergence of the technology necessary to develop large-scale applications, and now everybody seems to come up with a different definition. Among healthcare professionals, this term is generally used to define a new medical model proposing the customization of health care with medical decisions, practices, and products being tailored to the individual patient (2, 3). Once implemented on a large scale, precision medicine will amount to a Copernican revolution for a healthcare system still focused on reacting to people only after they present with disease and become "patients." In its place, the new paradigm will pursue the maintenance of health with targeted interventions on the basis of a personalized risk profile. Hence, the more fitting terminology "precision health."

The potential for this fundamental paradigm shift is unprecedented and impossible to estimate based on present knowledge. Indeed, traditional evidence-based medicine was built on the use of the double-blind randomized controlled trial, which is generally considered the gold standard for "representing things as they really are" and is used to confer scientific precision to clinical experimentation in an effort to achieve the objectivity of a laboratory model (4). In truth, a randomized controlled trial only provides information about what will work (or not) for a general or average population by extrapolating from measurements made in a randomly selected sample. But there is no such thing as a "general or average individual," because each one of us is unique at the genetic, biologic, psychological, and cultural level. The promise of precision health is: "I will find the prevention or therapy that is good for you as an individual."

However, such promise cannot be fulfilled without an accurate selection of the individual or population who will respond best to a particular intervention. This step requires a deep understanding of the biology of the disease and the identification of surrogate biomarkers that provide early indications of the impact of a target modification on the disease process, show therapeutic and toxic effects of management, and ultimately allow the development of more precise clinical guidelines (5). To be suitable for use in routine clinical practice, biomarkers must be easy and quick to obtain, relatively inexpensive, minimally invasive, and reproducible across various treatments and populations. Moreover, biomarkers should be physiologically relevant to the disease condition and able to predict relevant clinical outcomes with high accuracy. Although several putative biomarkers have been studied, their value for the diagnosis, prognosis, and therapy of asthma and chronic obstructive pulmonary disease (COPD) is still controversial. Of the few being used in specialized clinical settings, some, like fractional exhaled nitric oxide or serum periostin, have relatively low and inconsistent predictive accuracy (6), whereas others, like blood eosinophils and serum IgE, may not reflect tissue concentrations and therefore have limited physiologic relevance (7, 8).

In this issue of the *Journal*, Zhai and colleagues (pp. 302–312) (9) continue to build on previous clinical studies in which lower serum concentration of CC16 (club cell secretory protein 16) has been associated with the presence, risk, and progression of common obstructive lung diseases like asthma and COPD (10, 11). This protein is synthesized not only by typical club cells in distal airways but also by nonciliated airway secretory cells in large airway superficial epithelia that express MUC5 (mucin 5) genes (12), and changes in its serum concentration are not specific to obstructive disease but rather reflect multiple causes of lung damage (13). Being measured in serum using a commercially available ELISA, CC16 is quick and easy to obtain, relatively inexpensive, and minimally invasive.

This study has several strengths, particularly the combination of epidemiologic analysis of a human birth cohort with mechanistic experiments performed in an animal model, both showing a significant correlation between CC16 deficiency, decreased lung function, and increased airways resistance and reactivity. On the basis of the present and previous human data from the same investigators, CC16 seems able to predict relevant clinical outcomes starting at an early age (14). A more exciting finding comes from the studies in mice suggesting CC16 may have physiological relevance to the disease process attributable to increased airway remodeling, although causality cannot be determined from the data shown, and the interpretation of some results remains challenging.

In particular, because this protein has potent antiinflammatory and antioxidant activity, one would expect to find inflammatory markers in the airways and blood when CC16 is deficient, which is, in fact, the case for patients with asthma or COPD (15). Surprisingly, inflammatory cells, proinflammatory cytokines, mucin production, and other factors strongly associated with airway remodeling—especially transforming growth factor-β—were not increased in the airways of CC16-deficient mice, which casts some doubt on the suitability of the mouse model to recapitulate mechanisms at work in humans with obstructive lung disease.

Another important limitation of this work is the lack of an independent validation cohort. As noted above, it is indispensable for a biomarker to be reproducible across various populations and environmental conditions. Something that works in the Tucson Children's Respiratory Study cohort may very well not be useful in other populations. Therefore, the results and conclusions of this study need to be replicated in subjects from diverse racial, sex, age, and environmental categories, and normative benchmarks need to be generated before CC16 can be considered for use in routine clinical practice. Also important will be to address the "chicken versus egg" question—whether CC16 is indeed a cause or rather a byproduct of airway remodeling, as only the first instance would be amenable to replacement therapy.

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Despite the long way and many hurdles ahead, this study is an important step in the right direction. We hope that CC16 and similar biomarkers soon will help us understand better the pathophysiology of lung disease, provide early indications on the disease process, help develop actionable clinical guidelines, determine the population that will respond best to specific medications, and perhaps open the path to replacement therapy. For instance, the lung function of preschool children in the lowest tertile of serum CC16 could be closely monitored to detect subclinical remodeling before the progression to symptoms leads the patient to seek medical attention. Also, precise algorithms could be developed to tailor environmental interventions limiting biological (e.g., allergens, microbes) and inorganic (e.g., indoor/outdoor pollution) exposures and even intervene with early pharmacologic treatment or CC16 replacement.

In more general terms, CC16 and similar biomarkers represent the missing link necessary to finally connect past and present evidence-based medicine to a new healthcare paradigm. The recent launch of the NIH "All of Us" Research Program (https://allofus.nih.gov), aiming to enroll 1 million Americans to advance the promise of precision medicine and transform health care, promises to be the "tipping point" that will allow this approach to grow exponentially, leaping beyond genome sequencing into a wide array of solutions, services, and technologies that will progressively shift the focus of our healthcare system toward precision and prevention. ■

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Anabolic Medications for Muscle Wasting in Chronic Obstructive Pulmonary Disease

Is the Evidence Getting Stronger?

Muscle wasting in chronic obstructive pulmonary disease (COPD) is a significant problem that affects up to 30% of those with the disease (1). Muscle wasting results in limb muscle dysfunction, with the lower limbs affected more than the upper limb muscles (2). Quadriceps muscle wasting and weakness is associated with increased mortality (3, 4) independent of lung function. Quadriceps strength correlates with poor exercise tolerance (5), and an increase in quadriceps strength results in an increase in work capacity (6). The mechanism of this important comorbidity is complex and multifactorial (2). Myostatin, activin A, and activin B are important negative regulators of muscle mass, and they exert their negative effect on muscle mass by binding to the activin

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