Perspective: A test for those left behind

Sweat-chloride measurements could be used to develop and approve drugs for rare mutations in cystic fibrosis, says Steven M. Rowe.

The advent of highly efficacious therapies against cystic fibrosis is a stunning achievement. Although short of a cure, the use of drugs to restore the function of the faulty protein that causes the disease — cystic fibrosis transmembrane conductance regulator (CFTR) — is leading to major improvements in health.

Nearly a decade on from the introduction of the first CFTR modulator, these therapies have led to reduced levels of organ damage and chronic infection, while improving lung function, exercise capacity, nutritional status, quality of life and even survival. And because CFTR modulators are gradually being approved for use in young children and babies, their potential benefits could be even greater as they prevent extensive damage to organs such as the lungs and pancreas in early life. Multi-agent CFTR-modulator therapy can now help up to 90% of people with cystic fibrosis (those who have the F508del mutation on either or both of their *CFTR* genes), and there is a major impetus to expand the use of CFTR modulators to the remaining 10%.

However, there are challenges to the further development of these drugs. The conventional approach to developing and testing CFTR modulators would have us proceed with randomized controlled trials (RCTs) lasting 4–24 weeks and with a variety of clinical-outcome measures. But this standard of RCT will be increasingly difficult to achieve because of the small numbers of people with rare mutations who are being targeted. Furthermore, the standard measurement of lung function using spirometry (the FEV_1 test) is ineffective at detecting improvement in the increasing number of people with cystic fibrosis who have high lung function. These people will be left on the sidelines, waiting for the impossible study to be performed, despite the high likelihood that they could experience real benefit from treatment.

Regulatory science is beginning to address the challenge. Most notably, the approved use of the CFTR modulator ivacaftor was expanded in 2017 to include a small number of people with rare genetic variants on the basis of *in vitro* testing, a highly innovative decision by the US Food and Drug Administration. However, this alone is not sufficient, because thousands of *CFTR* mutations occur in only tiny numbers of individuals, who together represent the bulk of the untreated but potentially eligible population. Leaving this problem to clinicians, health-insurance companies and others to solve will be a slow and arbitrary process.

A tenable solution lies in sweat-chloride testing, the simple yet elegant diagnostic test that reflects CFTR function. Just as blood-pressure testing enabled the development of various anti-hypertensive agents to prevent a variety of cardiovascular ailments, sweat-chloride testing should become the equivalent in cystic fibrosis, allowing different CFTR modulators to reach people who remain very much in need.

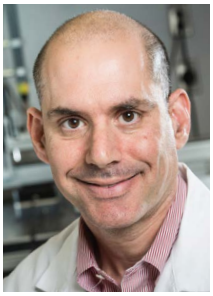
Sweat-chloride testing enabled the efficient early-phase development of CFTR modulators[1], and the sweat test provides an accurate estimate of CFTR function because CFTR acts to efficiently resorb chloride from the fluid released by the sweat duct. The absence of CFTR results in high chloride levels, a characteristic often first recognized by a salty taste on the skin. Because the sweat gland is not affected by progressive pathology, its reading of CFTR function remains accurate.

In the eyes of regulatory science, biomarker validation requires an intensive process, including definitive clinical experience across agents with different mechanisms. In the case of CFTR-modulator development, this process needs to be reconsidered. Aside from delaying access to current agents, the usual process will slow the development of alternative modulators for small groups of individuals with a high probability of substantive benefit. And such a barrier to progress inevitably increases cost and health disparities. This is particularly likely to be so in cystic fibrosis, given the higher prevalence of mutations that are not currently approved for treatment with CFTR modulators among people who are not of European descent (see https://cftr2.org).

Although the correlation of sweat-chloride tests with clinical outcomes on an individual basis has been complex, group data indicate a strong association with positive short- and long-term outcomes of CFTR-modulator therapy across agents and genetic mutations[2,3]. Importantly, sweat chloride has also been a faithful indicator of negative results in a variety of circumstances.

There are potential pitfalls. Rarely, sweat chloride could become uncoupled from CFTR function. That risk, however, should mainly be limited to drugs with atypical delivery to the skin versus other organs or to agents that unexpectedly alter sweat secretion — both of which are easily testable features[4]. Once this strategy is adopted, with the risks managed for a broad group of patients, individuals with rare mutations can be studied as a group.

The care of people with cystic fibrosis is in the middle of a major transformation, but a substantial minority are missing out on the benefits because the RCT model does not fit their case. The scientific community must rapidly adapt to these circumstances to maintain the marked pace of therapeutic research.



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