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New test promises quicker, more accurate evaluation for cystic fibrosis patients

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Researchers at National Jewish Health have identified a simple gene-based blood test that more accurately and quickly measures cystic fibrosis patients' response to therapy than current tests. The test, a measure of inflammatory gene expression, could improve patient care and help clear a backlog of promising medications now hung up in clinical trials. The researchers recently published the results of a small "proof-of-principal" trial in the online version of American Journal of Respiratory and Critical Care Medicine, and will also publish them in a future print issue.

"The currently accepted test, a measure of a patients' ability to exhale air, has several limitations that make it ineffective for some patients and not sensitive enough for clinical trials of many new medications," said Dr. Milene Saavedra, lead author of the study and Assistant Professor of Medicine at National Jewish Health. "By measuring the activity of genes associated with the immune/inflammatory response, we can get a more accurate picture of the biological processes occurring inside the lungs."

Cystic fibrosis is the most common lethal inherited disease in the western world, with about 30,000 patients in the US. Most patients die of respiratory failure generally in their 30s or 40s. Lung damage is caused primarily by chronic bacterial infections and the resulting severe airway inflammation. There is a critical need for new effective anti-microbial and anti-inflammatory medications to slow and/or prevent lung damage in young patients. Several promising therapies have gone through early stages of clinical testing but their progress is being hampered by the lack

of a sensitive measure of therapeutic response to medications.

Currently, response to medication is measured by how much air a person can rapidly exhale: forced expiratory volume in one second or FEV1. FEV1 cannot be performed effectively for all patients, especially young and very sick patients. Generally patients' FEV1 does improve when inflammation is reduced, but not all patients' FEV1 improves significantly, and changes can take weeks to months to show up. It can be prohibitively expensive to conduct phase 2 or phase 3 trials of medications long enough to detect the changes in FEV1.

National Jewish researchers thought white blood cells circulating in the blood might be a good source of biomarkers for a more sensitive and accurate test. White blood cells are the predominant cell type at sites of tissue destruction in CF patients' lungs. As they circulate through the lungs in the blood they encounter the inflammatory environment and alter their gene expression as a result. By measuring mRNA, scientists can identify which genes are being expressed and how strongly.

The researchers evaluated 18 CF patients who were suffering severe exacerbations of their disease. They withdrew blood before and after two weeks of intravenous antibiotic therapy. The severe exacerbation and antibiotic therapy served as a condensed model of illness and response to therapy; in these cases antibiotic therapy is usually successful, and patients' clinical symptoms and FEV1 both improve rapidly.

Using microarray gene analysis of the blood samples, the researchers identified 10 genes that differed significantly in their expression before and after therapy. Using real-time polymerase chain reaction and additional statistical tools, the researchers identified three of those genes that most accurately correlated with a positive therapeutic response: CD36, CD64 and ADAM9. CD36 and CD64 are genes associated with

cells' absorption of foreign organisms and cellular debris. ADAM9 is associated with tissue destruction that allows inflammatory cells to move through tissue. This process is also believed to contribute to permanent tissue destruction.

"The expression of these genes correlated with FEV1, other inflammatory markers, and various clinical factors," said co-author Dr. Jerry Nick, Associate Professor of Medicine at National Jewish. "When combined with FEV1, they offered a more accurate and sensitive measure of response to therapy than either alone. We believe they could be extremely useful in clinical care of patients and trials of new CF therapies."

The researchers are now conducting a trial of 60 CF patients to provide stronger statistical evidence for the power of CD36, CD64 and ADAM9 to diagnose a positive response to therapy by CF patients.

Source: National Jewish Medical and Research Center