Two-gene test predicts which patients with heart failure respond best to beta-blocker drug, study finds

Written by admin · October 15, 2012 @ 5:52 pm · Filed under Hot News, Morsani College of Medicine, News Releases, Research, USF Health Lead Story

Personalized medicine research at University of South Florida strikes early for heart genes

Tampa, FL (Oct. 16, 2012) – A landmark paper identifying genetic signatures that predict which patients will respond to a life-saving drug for treating congestive heart failure has been published by a research team co-led by Stephen B. Liggett, MD, of the University of South Florida.

The study, drawing upon a randomized placebo-controlled trial for the beta blocker bucindolol, appears this month in the international online journal ***PLoS ONE.*** In addition to Dr. Liggett, whose laboratory discovered and characterized the two genetic variations, Christopher O'Connor, MD, of Duke University Medical Center, and Michael Bristow, MD, PhD, of ARCA biopharma and the University of Colorado Anschutz Medical Campus, were leading members of the research team.

Dr. Stephen Liggett, who joined USF just four months ago to lead the University's Center for Personalized Medicine and Genomics, was a senior author of the landmark paper.

The analysis led to a "genetic scorecard" for patients with congestive heart failure, a serious condition in which the heart can't pump enough blood to meet the body's needs, said Dr. Liggett, the study's co-principal investigator and the new vice dean for research and vice dean for personalized medicine and genomics at the USF Morsani College of Medicine.

"We have been studying the molecular basis of heart failure in the laboratory with a goal of finding genetic variations in a patient's DNA that alter how drugs work," Dr. Liggett said. "We took this knowledge from the lab to patients and found that we can indeed, using a two-gene test, identify individuals with heart failure who will not respond to bucindolol and those who have an especially favorable treatment response. We also identified those who will have an intermediate level of response." The research has implications for clinical practice, because the genetic test could theoretically be used to target the beta blocker to patients the drug is likely to help. Equally important, its use could be avoided in patients with no likelihood of benefit, who could then be spared potential drug side effects. Prospective studies are needed to confirm that bucindolol would be a better treatment than other classes of beta blockers for a subset of patients with health failure.

Dr. Liggett collaborated with medical centers across the United States, including the NASDAq-listed biotech company ARCA biopharma, which he co-founded in Denver, CO. This genetic sub-study involved 1,040 patients who participated in the Beta-Blocker Evaluation of Survival Trial (BEST). The researchers analyzed mortality, hospital admissions for heart failure exacerbations and other clinical outcome indicators of drug performance.

"The results showed that the choice of the best drug for a given patient, made the first time without a trial-and-error period, can be accomplished using this two-gene test," Dr. Liggett said.

The genetic test discovered by the Liggett team requires less than 1/100th of a teaspoon of blood drawn from a

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patient, from which DNA is isolated. DNA is highly stable when frozen, so a single blood draw will suffice for many decades, Dr. Liggett said. And since a patient's DNA does not change over their lifetime, as new discoveries are made and other tests need to be run, it would not be necessary to give another blood sample, he added.

This is part of the strategy for the USF Center for Personalized Medicine and Genomics. The discovery of genetic variations in diseases can be targeted to predict three new types of information: who will get a disease, how the disease will progress, and the best drug to use for treatment.

"In the not too distant future, such tests will become routine, and patient outcomes, and the efficiency and cost of medical care will be impacted in positive ways. We also will move toward an era where we embrace the fact that one drug does not fit all," Dr. Liggett said. "If we can identify by straightforward tests which drug is best for which patient, drugs that work with certain smaller populations can be brought to the market, filling a somewhat empty pipeline of new drugs."

This approach is applicable to most diseases, Dr. Liggett said, but the USF Center has initially concentrated on heart disease, because it is a leading cause of deaths, hospitalizations and lost productivity in the Tampa Bay region and Florida. Dr. Liggett is a recent recruit to the USF Health Morsani College of Medicine, coming from the University of Maryland School of Medicine. His work at USF has been supported by several National Institutes of Health grants and $2 million in funding from Hillsborough County.

Heart failure is characterized by an inability of the heart muscle to pump blood, resulting in dysfunction of multiple organs caused by poor blood and oxygen flow throughout the body. An estimated 6 million Americans are living with heart failure, and more than half a million new cases are diagnosed each year. About 50 percent of patients diagnosed with heart failure die within five years. The economic burden of heart failure in the United States is estimated at $40 billion a year.

Article citation:
Christopher M. O'Connor, Mona Fiuzat, Peter E. Carson, Inder S. Anand, Jonathan F. Plehn, Stephen S. Gottlieb, Marc A. Silver, JoAnn Lindenfeld, Alan B. Miller, Michel White, Ryan Walsh, Penny Nelson, Allen Medway, Gordon Davis, Alastair D. Robertson, J. David Port, James Carr, Guinevere A. Murphy, Laura C. Lazzeroni, William T. Abraham, Stephen B. Liggett and Michael Bristow, "Combinatorial Pharmacogenetic Interactions of Bucindolol and β_1, α_{2C} Adrenergic Receptor Polymorphisms," PLoS ONE 7(10): e44324. doi:10.1371/journal.pone.0044324

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