

Davidian explores the role of statistics in personalized medicine

By Robin Arnette

Determining the optimal treatment strategy for an individual patient, or personalized medicine, has generated a huge amount of interest during the last 10 years. Much of the attention grew from the hope that a better understanding of the human genome would lead to targeted medical treatments. But, according to biostatistician Marie Davidian, Ph.D., better statistical methods must be developed before doctors and patients reach that goal.

NIEHS Biostatistics Branch Chief Clarice Weinberg, Ph.D., hosted Davidian, (<http://www.stat.ncsu.edu/people/davidian/>) when she came to campus May 8 as the featured speaker for the 2013 Distinguished Lecture Series. Davidian is a William Neal Reynolds Professor in the Department of Statistics at North Carolina State University (NCSU). During her talk, she focused on the role statistical methods will need to play in developing personalized treatment strategies.

Davidian began her seminar by encouraging the audience to expand its definition of a medical treatment.

“We normally think of a [prescription] drug when we think of a treatment, but it could be a biologic, medical device, surgical procedure, or a behavioral intervention,” Davidian said. “Everything from cholesterol medication and an artificial limb, to chemotherapy and cognitive therapy, could be considered a treatment.”

Clinical trials — the gold standard for evaluation

Davidian said, the U.S. Food and Drug Administration evaluates treatments, before they enter the market, by testing a product’s safety, efficacy, and effectiveness. Surprisingly, it wasn’t until 1969 that congressional legislation mandated the use of clinical trial evidence for regulatory approval of a new treatment product in the U.S.

Today, two controlled, randomized clinical trials are required for final treatment approval, and it’s at this juncture that statisticians are most needed. Davidian maintained that the assessment of effectiveness, evaluated through standard statistical methods, boils down to the comparison of average outcomes between, or among, treatments. For example, if clinicians are testing treatments A and B, the classical analysis asks whether the average outcome for all of the patients who took treatment A is different from, and better than, those who took treatment B.

While comparison of average outcomes might be sufficient for regulatory purposes, knowing that one treatment is better, on average, than another may not be too informative for treating individual patients. Genetics, physiological, and demographic characteristics; previous medical history; and current health status influence response, and this heterogeneity dictates that each patient may require a slightly different treatment. Davidian said, researchers are thus often interested in identifying subgroups of patients that share certain characteristics, such as a specific gene mutation, who may benefit from being treated a certain way.



“2013 is the international year of statistics, so I encourage you to visit the [Statistics2013 website](http://www.statistics2013.org/), (<http://www.statistics2013.org/>) because there is a treasure trove of information about the profession,” Davidian said. “Organizers from the five major statistical societies built the site and have done a tremendous job in promoting the discipline.” (Photo courtesy of Steve McCaw)



Weinberg said, “As current president of the American Statistical Association, she [Davidian] is communicating the need to let solid statistical principles guide our efforts in turning big data into actionable inferences.” (Photo courtesy of Steve McCaw)



NIEHS Developmental Neurobiology Group lead researcher Patricia Jensen, Ph.D., left, and Deputy Scientific Director William Schrader, Ph.D., attended the talk. During the question and answer session, Schrader asked if medicines that have previously failed other clinical trials are being re-evaluated to determine if they work for a certain subgroup of patients. (Photo courtesy of Steve McCaw)

Identifying a treatment regime

Davidian said that, in clinical practice, physicians use their judgment to identify the appropriate treatment from a number of available options. She and others use statistical research to optimize that process, by developing sets of evidence-based rules, called treatment regimes, that guide doctors in their treatment decisions (see [text box](#)).

She also described recent work that used data from participants in a single study, who received treatments at two or more key decision points in the disease process, to develop optimal treatment regimes. Clinical trials, known as sequential, multiple assignment, randomized trials (SMART), are ideal studies for collecting such data. In SMART trials, patients are randomized at each decision point to receive one of the possible treatment options.

Davidian and other colleagues at NCSU, the University of North Carolina at Chapel Hill Department of Biostatistics, and Duke University Department of Biostatistics and Bioinformatics, have joined forces to develop statistical methods to identify the best treatment regimes for cancer. With funding from the National Cancer Institute, this collaboration will determine how to design multiple randomized trials to collect the information necessary for personalized medicine.

As a biostatistician, Weinberg understands the importance of statistics in handling the enormous amount of information that can be produced by clinical trials. She sees Davidian's contribution as crucial to developing a better understanding of how to treat chronic disease.



Having analyzed data from several clinical trials, Michael Fessler, M.D., left, of the NIEHS Laboratory of Respiratory Biology was particularly interested in Davidian's lecture. (Photo courtesy of Steve McCaw)

Employing statistics to find the best treatment

The rules that comprise a treatment regime correspond to each decision point in the disease process. As an example, Davidian gave the following hypothetical rule for the use of induction chemotherapy in breast cancer patients.

She said, "Suppose there are two options, which I'll call chemotherapy 1 (C1) and chemotherapy 2 (C2). If the age of the patient is less than 50, and the progesterone receptor (PR) level is less than 10, give C1, otherwise C2."

Davidian's research is focused on developing rules based on data that input all information available on a patient and output the best treatment for that patient. If "x" is all of the information available, C1 equals "0," and C2 equals "1," she uses statistics to determine rules "d." For example, the rule above would have the form:

$d(x) = 0(C1)$ if age <50 and PR level <10

$d(x) = 1(C2)$ otherwise

"You can think of an infinitude of possible rules," Davidian continued, "but the goal is to find the rule leading to the best outcome. We are developing statistical methods to do this."

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