Clinical Chemistry

Commercial Immunoassays in Biomarkers Studies: Researchers Beware!

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Guest:
Dr. Nader Rifai is the Editor-in-Chief of *Clinical Chemistry* and a Professor of Pathology at Harvard Medical School and the Director of Clinical Chemistry at Boston Children's Hospital.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. In the U.S., testing by medical laboratories is most often performed using commercial procedures that have been approved by the U.S. Food and Drug Administration as in vitro diagnostic devices. But many cutting edge procedures are developed by laboratories themselves, so-called lab-developed tests.

The components used in these procedures may well be of uncertain providence or quality, and an editorial in the October issue of *Clinical Chemistry* addresses the issue.

The lead author was Dr. Nader Rifai, the Editor-in-Chief of *Clinical Chemistry* and a Professor of Pathology at Harvard Medical School, and the Director of Clinical Chemistry at Boston Children's Hospital. Dr. Rifai is our guest in this podcast.

Doctor, what drove you to write this opinion piece?

Dr. Nader Rifai: Well, in the past couple of decades our research focused on biomarkers and their potential utility in predicting future disease; diseases like diabetes, cancer, and heart disease.

So for example, in the past two decades when we were looking at the role of inflammation in cardiovascular disease, diabetes and hypertension, the so-called modern diseases, we were not only interested in examining established markers like CRP, IL-6, TNF-ά, but also we wanted to look at novel ones that reflect different aspects of the disease, like CD40 ligand and matrix metalloproteinases and others.

So for a novel marker, you try to see if there is a commercial source to get it, otherwise you will have to set up your own assay, which is by the way, not a trivial issue. It's extremely time-consuming and very costly.

So recently we wanted to look at several very new markers, and to our surprise we found a commercial source from China that can measure them, not only in human, but in a variety of other species.

So we got those kits. The problem is none of them actually worked. So we wasted a lot of money, time, and valuable samples, and the more really we looked into that company's products, the more suspicious we became. Something clearly is not right.

Then last summer there was an interesting commentary in *Nature* from a cancer researcher at Cambridge University entitled *'A Recipe for Disaster,'* where the researcher described her nightmarish experience when she purchased chemically synthesized stretches of RNA from a company where not all the required or needed information were disclosed, so as a result she wasted a year of her laboratory's time.

And that's when we thought that perhaps our experience is not unique and we should bring it to the attention of biomarker researchers and that's why we ended up writing this editorial.

Bob Barrett: How significant is this problem?

Dr. Nader Rifai: Well, it is indeed a significant problem, mainly because biomarker research is very, very active area at the present time.

So let's take, for example, NIH. NIH has a database called the RePORT Database that they list all the grants that they fund.

So if you go on the RePORT Database and you look at the grants that have the term biomarkers in the title, in the past three years there have been 14,000 grants that have been funded, 4,000 of which only deal with biomarker discovery.

And during the same three year period, there have been 140,000 articles that have been posted on PubMed that have the term biomarker in the title. So it is an extremely active area of research.

And if you look at the biomarker pipeline, which is the process that every novel biomarker has to travel, mainly from the discovery stage to clinical utility, there are four steps: the Discovery, Qualification, Verification, and finally Validation. And these steps are very important in order to reduce the false positivity of these markers.

The Validation step, the last step that I just mentioned, at the present time involves the use of immunoassays. So if the immunoassay you use in this step is poor, then it could derail a promising biomarker or send the investigators down the wrong path.

Bob Barrett: Well, just for curiosity, just between you and me, how expensive are those kits?

Dr. Nader Rifai: Well, the kits from the company of concern are not really cheap. They range from $800-1,200 each, and bear in mind, that's only for 40 measurements. And this price is about twice the cost of U.S. produced kits. So they are not cheap at all.

Bob Barrett: Well, on the basis of what you have said here, what should biomarker researchers be doing?

Dr. Nader Rifai: I advise investigators before processing anything just to look at the package insert on the company's website. The package insert should contain information about the characteristics of the assay, description of the antibodies used, for example, the source of the reference materials, and many other analytical measures that we look at in order to determine how well an assay works, such as the sensitivity, the cross-reactivity, repeatability, interference, et cetera.

And if the information is incomplete or unavailable, that should raise a flag. It is a bad sign. If the information was not provided upon request, then the kit should not be purchased.

If the information is available, it is still the responsibility of the investigator to fully evaluate the analytical performance of the kits prior to use.

So one has to remember that the fact the kit is expensive, that doesn't mean the kit works. And if the investigator is not familiar with the analytical evaluation process, which is very likely, then they really should consult a colleague clinical chemist.

Bob Barrett: How widespread has this problem become?

Dr. Nader Rifai: Unfortunately, the problem is widespread at the present time, because the same kit now is sold directly from several parent companies in China. But what is more concerning is the availability of these kits now from several reputable suppliers in the United States and in Europe.

So it's very difficult for investigators to know the actual origin or source of the purchased kits.

Bob Barrett: Well finally, Dr. Rifai, what do you hope to accomplish with this article?

Dr. Nader Rifai: Well, my hope is really to raise awareness about this problem. Raise awareness about this problem among the funding agencies, among the biomarker researchers, clinical investigators, as well as journal editors.

Bob Barrett: Dr. Nader Rifai is the Editor-in-Chief of *Clinical Chemistry* and a Professor of Pathology at Harvard Medical School and the Director of Clinical Chemistry at Boston Children's Hospital. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!