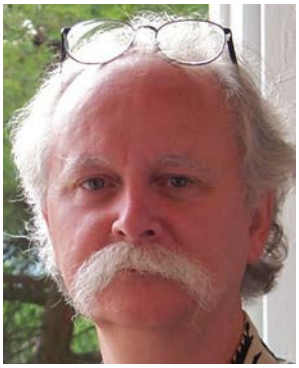
Clinical Chemistry

# The Riddle of Protein Diagnostics: Future Bleak or Bright?



**Article:**
L. Anderson.
*The Riddle of Protein Diagnostics: Future Bleak or Bright?*
Clin Chem 2013;59:194.
http://www.clinchem.org/content/59/1/194.extract

**Guest:**
Dr. Leigh Anderson is head of the Plasma Proteome Institute in Washington, DC.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Biomarker research is at the forefront of the quest towards personalized medicine. It's hoped that the discovery of new biomarkers will aid in better understanding of disease and in turn will lead to improved stratification of individuals at risk and to disease prevention. It is believed that over $1 billion has been spent over the last three years on biomarker discovery, yet the impact on clinical diagnostics so far has been unimpressive.

An editorial, published in the January 2013 issue of *Clinical Chemistry*, examines this situation. Dr. Leigh Anderson was lead author of that editorial and he is our guest in this podcast.

Dr. Anderson heads the Plasma Proteome Institute in Washington, DC, and has been involved in exploring plasma proteins of diagnostic importance since 1977.

Doctor, the search for new protein biomarkers is generating a lot of scientific interest. Is research funding following this interest?

Dr. Leigh Anderson: Well, it has in recent years. There has there has been something like a billion dollars devoted to the quest for biomarkers if you define that as grant funding, which mentions the word protein biomarker somewhere in the grant application or the summary. So it's a very significant amount of funding so far and the appetite for this appears to be continuing in the current rounds of funding.

Bob Barrett: So why aren't we seeing many new diagnostic protein tests?

Dr. Leigh Anderson: This is a really important question that has exercised a number of good minds to date. One option of course is that there aren't any more good biomarkers to be discovered and this seems implausible and also I think is missing the real point.

From my point of view, the key reason why we're not seeing new tests all the way through clinical use as protein biomarkers evolve, is that the method of taking a candidate biomarker which is the result of a discovery, proteomic study for example, and progressing it through to a clinical test, that pipeline has a gap in the middle, which is at the stage of verification or validation as it's currently called, which is the stage in which a candidate biomarker that appears to be disease related is actually tested in a large number, for example, a 1000-1500 samples, large enough to make a definitive statement with respect to the clinical utility. And those studies at this stage simply are not being done and that's the primary reason why we're not seeing the new protein tests come out.

Bob Barrett: Can we just blame all this on the FDA?

Dr. Leigh Anderson: That's an extremely attractive possibility, but in this case unfortunately it appears not to be the real answer. In fact I've asked the FDA whether it can be blamed on them and they say no in fact it's not their fault.

I tend to agree because the regulatory limitations are not the key ones at this stage. It's not the simply the FDA who are not taking forward a lot of new protein tests, it's a diagnostics industry itself, the real in vitro diagnostics industry that provides the hospital platforms that do these tests in real clinical use.

They're not convinced because they're not seeing sufficiently persuasive clinical data, and in this case that means primarily studies with enough samples, to convince them that it's worth spending that $3-$5 million per protein analyte that is required to generate an FDA-approvable test. The data just isn't good enough so far to justify that.

Bob Barrett: Where do biomarker researchers find appropriate clinical samples?

Dr. Leigh Anderson: Well that's another fascinating question. Unfortunately, most people in the biomarker research business so far are really on the technical side of proteomics looking to see how many proteins they

can see and they're not specialists in particular medical conditions or therapeutic areas. And as a result there is a tendency too often to say, well, who do I know, who is the good friend of mine or who has the lab next door to mine and has some samples that I could work on.

These are called samples of convenience really and often they are interesting to study, but they're simply not structured in such a way that they answer a definitive clinical question.

In order to answer a clinical question, which is of interest to the clinicians, appropriately, requires finding samples which are structured in such a way-- in other words controls matched with disease related samples and potentially confusing disease state samples-- structured in such a way that it takes time and effort and a lot of persuasion to extract those samples from the people who have them. And that's a level of effort and commitment that unfortunately the proteomics community has been lacking in so far in this quest to find the appropriate clinical samples.

Bob Barrett: Isn't there a public database out there of good sources of clinical samples for biomarker studies?

Dr. Leigh Anderson: There are beginning to be efforts to generate such a database. You would think that given, and in this case it really is billions of dollars that are spent on collecting high quality clinical specimens, that there would be general recognition of the need for such a broad database, so that if one identified the clinical question, it would be a matter of consulting the universally available resource to find out which really are the best of specimens or more importantly do the specimens even exist at this point to address a particular critical question.

Unfortunately, we don't really have general availability of such a database at this stage, although people are talking about it sufficiently, so that one can assume that it is going to be done.

I believe that the efforts to generate this kind of an index of available resources are perhaps more advanced in Europe, because of the structure of the government health care and the availability of patient records generally, more advanced in Europe than those efforts are in the US so far. But I believe that that will progress rapidly in the next several years.

Bob Barrett: Dr. Anderson, what is the Zolg number and why is it a problem in biomarker research?

Dr. Leigh Anderson: Well, every important concept has to have a name and for better or for worse the name, the last name of Werner Zolg, who was the head of proteomics at Roche Diagnostics, has been attached to the notion that if you can't analyze something on the order of 1500 samples by an assay, which would characterize a candidate biomarker, then you can't really determine whether that biomarker has a realistic chance of making a major clinical impact. And this was a number that Werner Zolg mentioned in a seminar at the NIH some years ago in which he was bemoaning the fact that the appropriate sample resources were not generally available and the case he was talking about particularly for looking at lung cancer diagnostics. But he just made the statement that if you can't run 1500 samples, don't come and talk to me about your candidate biomarker, because I know that you won't know whether it's really going to make a clinical difference.

And as a means of making a memorable figure which would stick in the minds of the proteomics community this has come to be called the Zolg number and it's something which is rarely been achieved. In fact, of the 20,000 or so published accounts of protein biomarker research over the last 10 or 15 years, we can really only identify three or four of those 20,000 papers that actually included the analysis of a Zolg numbers-worth of patients samples. So it's something which is rarely been attained, but is going forward absolutely critical.

Bob Barrett: Well, finally, doctor, your editorial title asks if the future is bleak or bright, so let's have it, is the future bleak or bright?

Dr. Leigh Anderson: Well, I really wish I knew. It's like knowing the question of whether one is going to win the lottery. In reality I believe that it is bright and the reason is, because we're becoming much better educated about where the appropriate samples are going to come from, how many we need to be able to analyze, and what kinds of technology are particularly appropriate for attempting to analyze the putative biomarkers that we've got and see which one are going to have real clinical value as people become more expert in doing this at the level of sophistication that's required.

I believe that we have finally passed the tipping point at which a significant number of new protein biomarkers that address previously unmet clinical needs is going to start to appear. And so I'm a believer that the future is bright, but until we actually have a flood of new really important protein biomarkers of course that's a -- that's a matter of debate and opinion. But my opinion is that it's bright.

Bob Barrett: Dr. Leigh Anderson is head of the Plasma Proteome Institute in Washington, DC. He's been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.