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

The current era of genomics, proteomics, and metabolomics is projected to lead to the discovery of many novel candidate biomarkers for cardiovascular disease. One such marker that is gaining momentum in diagnostic significance is Growth differentiation factor 15 or GDF15.

A paper published in the January 2012 issue of '*Clinical Chemistry'* by Dr. Anand Rohatgi and colleagues from the University of Texas, Southwestern, demonstrated the strengths of this marker in a prognostic setting. But two major questions remain. What biological insights can be gathered, and second, what is the clinical utility of measuring GDF15?

Attempting to answer those questions is Dr. Jennifer Ho, a cardiologist at the Massachusetts General Hospital who wrote an editorial published in the same issue of '*Clinical Chemistry'* on the significance of this marker. Dr. Ho is our guest in this podcast.

Doctor, in the current era of genomics, metabolomics, and proteomics, what do you look for to evaluate the significance or relevance of a new biomarker, such as GDF15?

Dr. Jennifer Ho: Oh I think this is a very difficult issue with so many emerging biomarkers, but there are some fundamental questions that I think are important considerations.

I think as clinicians, really, biomarkers serve two potential roles for us. Number one, they can provide insights into the pathophysiology disease, and number two, they can aid in clinical decision-making by clarifying diagnosis, prognosis, or response to therapy. In all three cases they can help us sort of risk stratify patients.

So the two questions that I ask myself usually are number one, what biological insights can be gathered, so can we learn anything new about the underlying pathophysiology, and can that help in form our treatment.

So for example, the prime example here in cardiology is cholesterol testing, so we can check so much cholesterol, if it's high we can start therapy that's targeted at the underlying pathway. We know that cholesterol is involved obviously in the process of atherosclerosis and the underlying disease.

The second question that I usually ask is, what is the clinical utility of a new biomarker, and this is more often than not

 

the more important issue and the evaluation of the new biomarkers coming out; and the main issue really here is, does it add new information to help risk stratify a patient, and can this information help the clinician manage patients.

And one such example in today's era of cardiology is, the use of cardiac troponins in patients with suspected acute coronary syndrome. So a positive troponin for example would help inform clinical decision making and guide therapy, for example, it may prompt sooner administration of glycoprotein IIb/IIIa inhibitors or early cardiac catheterization. So those are sort of the two things that I would look for when examining a new biomarker.

Bob Barrett: Let's turn the discussion over to GDF15, explain what that is, and in thinking about some of the questions you highlighted, what biological insights can we takeaway, and what's the clinical utility?

Dr. Jennifer Ho: So GDF15 or Growth differentiation factor 15 is a cytokine. It's part of the transforming growth factor beta superfamily, and it's a stress-responsive cytokine, meaning that certain triggers like cardiac ischemia and pressure overload can up-regulate its expression.

It's really in animal models, GDF-15 appears to have a protective effect and that's been shown via probably anti-inflammatory and anti-hypertrophic effect. But in contrast, in clinical studies, including the Dallas Heart Study paradoxically higher levels are associated with a worse prognosis.

In the Dallas Heart Study for example, it was associated or higher levels of GDF15 were associated with all cause in cardiovascular mortality. So this to me indicates that GDF15 appears to be more of the marker of the underlying disease process rather than a true mediator of the disease, so it's much like the natriuretic peptides in that way.

The clinical utility of GDF15 really remains unclear, and I think there are future studies to be done to really kind of determine what its use would be for the clinician.

Bob Barrett: You talked briefly about newer statistical metrics that can help us assess the performance of a new biomarker. Well, first of all, what are some of the standard measures of biomarker performance and how do they fall short?

Dr. Jennifer Ho: Well the most basic criteria is that the biomarker is associated, first of all, with the outcome of interest and that obviously is the basis of this study itself and that this association is independent of other potential confounding factors.

The next thing that we usually look at is, discrimination or the ability of a marker to distinguish those who will get the disease from those who will not and the metric that really is most essential to this idea is the c-statistic, or the area under the Receiver Operating Characteristic curve, and this is a statistical metric, which accounts for both the sensitivity and the specificity of a test or a new biomarker.

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And the values really range from 0.5, which is basically an unformative biomarker that's no better than say a coin toss to a 1.0, which is sort of a perfect biomarker, that will predict a disease in everyone who is going to get disease and no disease in everyone who is never going to get disease.

So what we often look at is how the c-statistic changes with the addition of a marker to a set of traditional variables that we already know to be associated with the outcome.

For example, in the Dallas Heart Study, a risk prediction model for mortality including only clinical factors had a c-statistic of 0.822 and with the addition of the new biomarker GDF15 this increased to 0.839, and although this was a statistically significant increase in the c-statistic, clinically, it's really unclear whether an increase of 0.017 in the c-statistic is meaningful, and this is sort of a modest increase at best. And this brings up some of the shortcomings of the c-static.

Once you have several powerful variables that are included in the base model, and the c-static is already relatively high, say above 0.8 or so, it's really quite difficult to get further increases in a c-static, no matter what else you add into the model, and so that's one of the short falls of the c-static.

Bob Barrett: And doctor, what are the newer metrics and how can they be interpreted?

Dr. Jennifer Ho: The newer approaches have really tried to focus on the impact of new biomarkers on clinical decision-making and really how they help reclassify someone's risk. So one of the newer metrics is the NRI or the Net Reclassification Improvement. It basically splits the patient population into those who ended up having the disease or had events and those who did not and for the groups that did have disease or did have events, it then looks at individuals that were up-classified in risk with a new marker and those are considered correctly classified, and then it looks at those that were down-classified in risk and calls them incorrectly classified. And thus, sort of the vice versa thing for people that didn't develop disease or they had – what we callnon-

 

events and the NRI is essentially a summary of both of those things.

A thing to keep in mind is that the NRI really depends on clinically meaningful categories of risk. So for example, we use the adult treatment panel guidelines to group predicted ten-year coronary heart disease risk into three categories. So we say, someone with a predicted risk less than 10% has a low risk, those between 10% to 20% have intermediate risk, and those with a greater or equal to 20% risk are at high risk for coronary heart disease.

And these categories actually help us as clinicians to determine what the LDL cholesterol treatment goal should be for any given individual. So these are meaningful categories in that they actually help us guide medical management.

The problem really is that for most outcomes that we look at with new biomarkers that there really are no accepted equivalent meaningful risk categories, for example, if we look at a biomarker predicting ten-year mortality, we don't know what could be considered low risk. Is it less than 1% or is it less than 5%. This is really not clear.

The other problem with category-based NRI is that it dependant on the number of categories and also the choice and cut points. For example, you could imagine that if you group people into only two categories, you would probably get a lower NRI, then if you group people into five different categories because you allow essentially for more movement between categories, if you have more categories. And so the category-based NRI was extended to what's now called the category-free NRI, which is probably the most objective as versatile measure in examining biomarker performance, and this can be more easily compared across studies, and can be used for outcomes which don't really have well-defined categories to start with and there basically any up or down classification of risk is counted.

Unfortunately, here it's less clear how clinically meaningful that up and down classification and risk is. For example, if you move somebody's risk from 5% to 5.1% with a biomarker versus if you move somebody's risk from 5% to 20% with a new biomarker, that's obviously a big difference but, in looking at the category-free NRI, these individuals would be essentially classified as equal.

So in order to address this, some people have stared recalculating the category-less NRI to define what we mean exactly by a change in risk, for example, we can calculate the NRI requiring a given change to exceed for example a change in 1% of the predicted risk or a change in 2% of the

predicted risk, so we actually have an increment that might be clinically a bit more meaningful.

In summary, the NRI and some of the other metrics that, we didn't really get to discuss here including the integrated discrimination improvement have all evolved to help us evaluate the performance of new biomarkers, and no one measure can really be taken in isolation because they each have their pros and cons, but all taken together we can get a better sense of the performance of a biomarker.

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Bob Barrett: Doctor, your editorial was entitled '*GDF 15: The Canary in the Coal Mine*', why is this a canary in the coal mine and how relevant is this to the GDF15 discussion?

Jennifer Ho: Well early coal mines actually had no ventilation systems, and so mining workers used to carry down caged canaries into the tunnels with them as early warning signs, and if there were any toxic gases like methane, or carbon-monoxide, the canaries would become sick or die first and basically send a warning signal for the miners to escape.

So really the way we intended to use it here is that what we don't know about GDF15 yet is whether it can act as the proverbial canary in the coal mine, in other words, if your GDF15 level is high, can that actually change medical management, can that prompt initiation of certain therapies or can that make us be more aggressive about lifestyle modification, or is GDF15 simple a harbinger of bad outcomes without really any specific therapeutic implication? The answer to those two questions is really unclear at this point.

Bob Barrett: Well finally doctor, what further evidence needs to be seen before we can decide whether GDF15 is a clinically useful biomarker?

Jennifer Ho: That's a great question. I think clearly GDF15 is a marker of worse prognosis, but the clinical utility is still unknown. I think one of the next steps would be to look at it in combination with other biomarkers, so any one biomarker may not change risk prediction by all that much but together in a multi-marker approach. We might get a lot more information about individual risk.

The other thing that we don't know anything about is what specific therapies if any might be useful in people with increased GDF15 levels, and in order to really get at this we need to understand more about the biological pathways that are involved.

Bob Barrett: Dr. Jennifer Ho is a cardiologist at the Massachusetts General Hospital. She has also been our guest in this podcast from '*Clinical Chemistry*'.

I am Bob Barrett. Thanks for listening!

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