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Tumor Microenvironment–Released Peptides: Could They Form the Basis for an Early-Diagnosis Breast Cancer Test?

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Guest:
Dr. Eleftherios P. Diamandis is professor and head of the Division of Clinical Biochemistry at the University of Toronto.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I'm Bob Barrett. The January 2014 issue of *Clinical Chemistry* is devoted to the area of women's health. It includes a multi-center report on the application of measuring the circulating products of the proteolytic enzyme carboxypeptidase-N for the early detection of breast cancer. Accompanying that paper was an editorial by Eleftherios Diamandis on the tumor microenvironment and if released peptides could form the basis for early diagnosis breast cancer tests. Dr. Diamandis is professor and head of the Division of Clinical Biochemistry at the University of Toronto. He's our guest in today's podcast.

Dr. Diamandis, there is widespread opinion that cancer biomarkers have not fulfilled their potential. Why is that?

Dr. Diamandis: Well most of the cancer biomarkers that we are using today in the clinic have been discovered more than 25 years ago. Unfortunately, despite the optimism that newer and improved cancer biomarkers could be discovered with the revolutionary new technologies of genomics, proteomics, epigenomics, metabolomics and other -omics - the reality is that clinically useful biomarkers have not been recently discovered. I believe that the main reason is that we have not been able to identify tissue in cancer specific molecules which are informative and they are elevated in the blood early during cancer development and progression.

This may be that such molecules either do not exist or that they are in such low abundance in the circulation that we could not see them with the current techniques. The hope is that we further improve analytical technologies. It may still be possible to find informative biomarkers in the future.

Bob Barrett: Are there any good and clinically useful biomarkers of breast cancer available at present?

Dr. Diamandis: Well, unfortunately not. There is one marker which was discovered more than 25 years ago, what is known as cancer antigen 15-3. Unfortunately, this marker has very

poor performance characteristics such as very low sensitivity for early disease detection making it unsuitable for diagnosis or screening. Clearly, newer serum biomarkers for breast cancer are desperately needed.

Bob Barrett: What about the role of mammography for breast cancer screening and how does that compare to laboratory diagnostics?

Dr. Diamandis: Yes, as you know, mammography is widely used for breast cancer screening. Unfortunately, it is not a perfect method since it is not very informative in younger women; and for older women, recently, data have shown that breast cancer patients identified by mammography do not gain a significant survival benefit versus those who have been diagnosed without mammography. Additionally mammography exposes a patient to ionizing radiation which may inflict some harm. The patients for whom mammography can contribute significantly are those with an increased risk for breast cancer.

Bob Barrett: The paper that appears in *Clinical Chemistry* proposes carboxypeptidase-N as a non-invasive early breast cancer diagnostic test. What are you thoughts regarding this study?

Dr. Diamandis: Well, we know for many years that proteolytic enzymes play a major role in cancer metastasis around the tumor microenvironment. These authors have shown that one of these enzymes, carboxypeptidase-N is produced of high amounts within the microenvironment of breast cancer, and that this activity is generating peptides that circulate in blood. The authors also used a highly sensitive mass spectrometry method to measure these peptides and compare them between patients with breast cancer and healthy controls. More importantly, they found elevations of six peptides which were more pronounced in early breast cancer. Well, taken at face value, these data suggest that the measurement of these peptides may form the basis for an early breast cancer diagnostic test by using a non-invasive technique.

Bob Barrett: What do you think are the major limitations of this study?

Dr. Diamandis: Well, the discovery data of Li et al., the authors of this paper, are based on a small number of patients. For example, a dozen patients per clinical group of controls, breast cancer over various clinical stages. Also reading this paper, I have seen a relatively large scatter of the concentrations of these peptides in breast cancer patients, which overlap with some controls. This of course means imperfect sensitivity and specificity. It may well be that this

test could be refined and further validated to become clinically useful, but we have to wait and see.

Bob Barrett: I have to say you sound a bit pessimistic about that, can you tell us why?

Dr. Diamandis: Well in my long career, I have seen publications of many reports especially on cancer biomarkers that show highly promising preliminary data, which then fail at independent validation stage. This is due to many reasons including initial sample selection biases to maximize the performance of the test, analytical methods which are not very reliable, biases in patient preparation and sample storage, and bioinformatics artifacts. All these parameters are not usually tightly controlled in preliminary studies. Further validations which are more carefully designed with much larger number of specimens - when these confounding variables are controlled - the results are weakened to a point where clinical applicability is not warranted. I thus want to wait and see how this test will evolve over time. For example, it could be refined to a degree that makes it clinically useful, or it will fail further validation. The judge for this will be time.

Bob Barrett: Dr. Eleftherios Diamandis is professor and head of the Division of Clinical Biochemistry at the University of Toronto. He has been our guest in today's podcast from *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.