

The parallel lives of prostate specific antigen in cardiac troponin assays

Eleftherios P. Diamandis^{1*}

¹Senior Scientist, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada.

Article Info

Author of correspondence:

Dr. Eleftherios P. Diamandis, Senior Scientist, Lunenfeld-Tanenbaum Research Institute;

E-mail: diamandis@lunenfeld.ca;

Address:

Sinai Health System, Toronto, Canada

Serum prostate specific antigen (PSA) is a cancer biomarker that is widely used for the diagnosis and management of prostate cancer (CaP). Serum cardiac troponin is used widely for the diagnosis and monitoring of cardiovascular diseases, including, myocardial infarction (MI). These two biomarkers are among the very best in clinical chemistry testing, in terms of clinical sensitivity and specificity. By comparing the developments of PSA and cardiac troponin biomarkers, it can be realized that they have important analytical and clinical similarities. Below, I mention briefly the analytical and clinical developmental milestones of these two biomarkers over the last 50 years. Please note that due to space limitations, I will not attempt to assign credit to those who played a role in the discovery and validation of either the PSA or cardiac troponin assays. Reviews on this subject have been published elsewhere (1,2).

Prostate Specific Antigen

PSA was isolated from prostate tissue in the 1970's and it was realized at that time that it is prostatic tissue specific (tissue specificity is a major advantage for any biomarker). In the early 1980's, a competitive radioimmunoassay for measuring PSA in serum was developed (sensitivity ~0.1 ng/mL or 100 ng/L, first generation assay) * and used in the initial studies which have shown that PSA is a far superior marker of prostate cancer in comparison to prostatic acid phosphatase, a test that was used at that time. PSA assays were adopted in clinical practice within only 3-4 years, something that is relatively rare in the tumor marker field. A few years later (early 1990's), a more reliable assay based on the "sandwich" principle was developed and it was used by many clinical investigators to study the value of PSA for the diagnosis of prostate cancer and especially, for prostate cancer screening of asymptomatic men. These first-generation PSA assays were able to quantify PSA in the serum of males (concentration is usually 1-4 ng /mL or 1,000-4,000 ng/L). In early 2004, large prospective studies have been initiated to examine the value of PSA in prostate cancer screening, but the outcomes, published a few years later, were, and still are, controversial.

In 1997, our group developed the first third generation PSA assay which was capable of measuring PSA down to 0.001 ng/ml (or 1 ng/L) (3). These third-generation assays opened the possibility that PSA could be used as a highly sensitive marker of prostate cancer relapse, and it is currently used for this purpose (Figure 1). Around the same time, the company MesoScale Diagnostics and others, extended the sensitivity of the PSA assay by two orders of magnitude (fifth generation assays; sensitivity 0.00001 ng/mL or 0.01 ng/L). This development allowed measurement of PSA in the serum of males as well in serum of almost all females (the source of PSA in females is the breast). This development revealed that PSA is an excellent marker of hyperandrogenism in women.

Cardiac troponins

Just like PSA, in the 1970's, researchers isolated troponin T and troponin I from cardiac muscle and they found that this antigen is highly specific to this tissue. Cardiac troponins proved to be superior in specificity to the protein that was used in that time for studying myocardial infarction, which was the CK-MB isoenzyme of creatine kinase. In the early 1990's the first immunoassays for measuring cardiac troponins were developed (first generation) (4) and have shown to have the ability to measure troponin in serum after myocardial infarction (but not in serum of normal men or women). These first-generation assays had sensitivities, like PSA, of around 100 ng/L and were used to confirm the clinical superiority of troponins over immunological CK-MB assays. Like PSA, in the mid-1990's, scientists developed higher sensitivity cardiac troponin assays, which allowed the detection of lower levels of cardiac troponins in the bloodstream, thus enabling detection of smaller and smaller cardiac infarctions. At the same time, many companies have engaged in developing highly sensitive assays for cardiac troponins and eventually reached detectability in the low ng/L range (third, fourth and fifth generation assays) (5). This development necessitated the change of reportable units of troponin from ng/mL to ng/L, to avoid reporting numbers with many zeros, for easier communication with clinicians. Current reference ranges using the 99th percentile in normal individuals, are now up to around 10 ng/L for women and up to 15 ng/L for men. The reference ranges are still different between assays of manufacturers of high sensitivity cardiac troponin assays. The clinical utility of the cardiac troponin assays is so valuable, that the current definition of acute myocardial infarction (AMI) is partly based on the changing levels of cardiac troponins (their kinetics), along with the combination of clinical symptoms. Hundreds of papers have been published on the clinical use of cardiac troponins for diagnosis and monitoring of myocardial infarction and other cardiac diseases. high sensitivity cardiac troponin assays. The clinical utility of the cardiac troponin assays is so valuable, that the current definition of acute myocardial infarction (AMI) is partly based on the changing levels of

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Concluding remarks

PSA and troponin assays have evolved from crude, semiquantitative immunoassays (first generation) to highly sensitive and specific tests (up to fifth generation), that have revolutionized the diagnosis and monitoring of patients with prostate cancer or heart diseases. Harmonization of results between assays from diverse manufacturers, is a major current and future step forward. My prediction is that these assays will likely remain in the menu of clinical chemistry testing for many decades, if not centuries. Do we need sixth-generation PSA and cardiac troponin assays? No, because the fifth-generation assays can comfortably and precisely measure these two biomarkers in almost all healthy and diseased men and women, including men whose prostate has been surgically removed.

Footnote

*Assay generations. Conventionally, the first developed assay for a biomarker is called "first generation". Subsequent generations usually have an approximately 10-fold increase in sensitivity.

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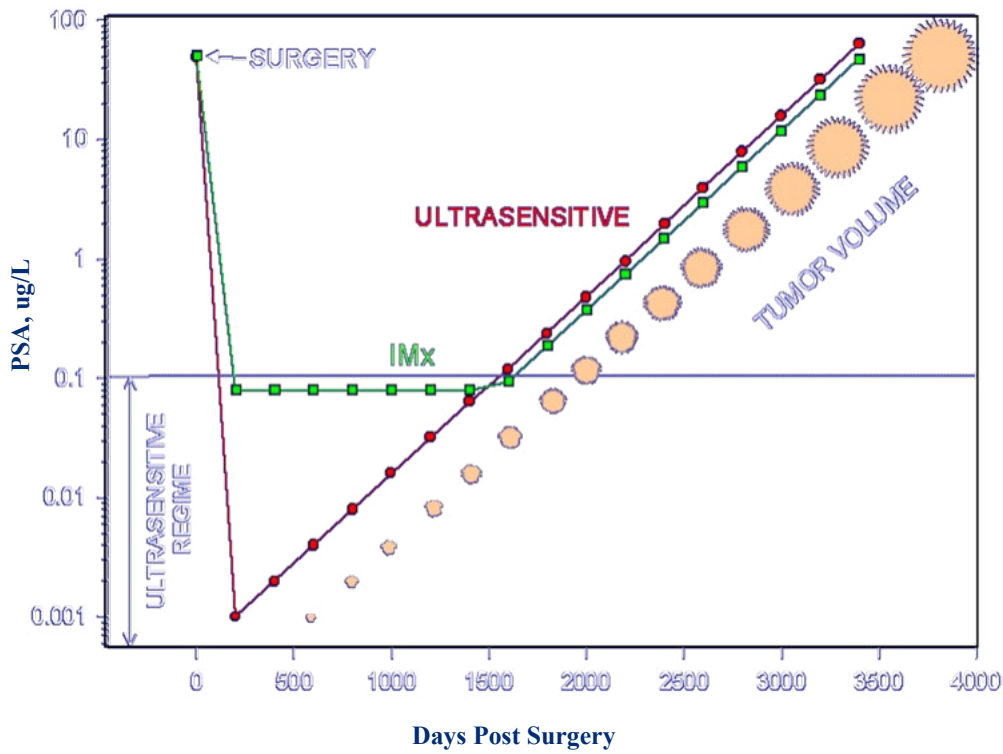


Figure 1: A hypothetical example of monitoring the progression/relapse of a prostate cancer patient after radical prostatectomy (surgery). Green dots represent a first-generation PSA assay (Abbott IMx). Red dots represent a third-generation assay, described in Ref. 3.