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PSA Test Is Misused, Unreliable, Says the Antigen's Discoverer

Eric J. Topol, MD; Richard J. Ablin, PhD, DSc (Hon)

DISCLOSURES

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*In this edition of Medscape One-on-One, host and Medscape Editor-in-Chief Eric J. Topol, MD, interviews **Richard J. Ablin, PhD, DSc (Hon), who first discovered prostate-specific antigen (PSA) in 1970**. At the time, Dr. Ablin and colleagues were trying to identify an antigen that was specific to prostate cancer. What Dr. Ablin identified instead was **that PSA was present not only in malignant prostates but also in benign prostates**. He did agree, however, that elevated levels of PSA might be useful in predicting a recurrence of prostate cancer in men who were thought to be in remission.*

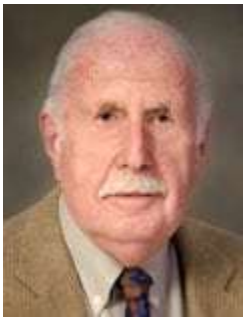
*It was much to Dr. Ablin's dismay that more than 2 decades later, in the mid-1990s, the US Food and Drug Administration (FDA) approved the use of PSA not only to test for recurrence of cancer, but also as a possible predictor of cancer. Since then, Dr. Ablin maintains, the United States spends billions each year administering a preventive prostate cancer screening test to men, using PSA, that **produces false positives in the majority of cases**. In his interview with Dr. Topol, Dr. Ablin explains why physicians and patients should proceed with caution when using PSA as a marker for preventive screening.*

The Discovery of Prostate-Specific Antigen

Eric J. Topol, MD

Eric J. Topol, MD: This is Eric Topol here for Medscape One-on-One, with Richard Ablin at the University of Arizona. Dr. Ablin has recently coauthored a book titled *The Great Prostate Hoax* (Macmillan, 2014).[1] This is a very interesting opportunity to speak with the discoverer of PSA. Welcome, Dr. Ablin.

Richard J. Ablin, PhD: Thanks very much. Having followed your work, this is a treat for me. I hope that in the course of our conversation, people and families will understand what they should know about prostate cancer moving forward, so thank you for this opportunity.



Richard J. Ablin, PhD, DSc (Hon)

Dr. Topol: Let's talk about your background. You were at Lake Forest College, and then at SUNY in Buffalo. You worked at the well-known cancer center at Roswell Park. You were in Chicago at Cook County for a while, and now you are at the University of Arizona.

Let's go back to 1970, around the time that you first came across what is now called PSA. What were your thoughts about it at that time?

Dr. Ablin: To be as brief as possible, in 1967 I had joined 2 urologists in Buffalo at a teaching hospital there (my background is immunology) who were working on an alternative treatment for prostate cancer called cryosurgery -- freezing instead of cutting. In the course of our studies, when we were freezing the prostates of experimental animals -- rabbits, dogs, baboons, rhesus monkeys -- we were observing an immune response similar to that seen following a vaccine. When we froze more than once, we saw a characteristic booster response.

When we were following up some of our clinical studies by looking at x-rays, we saw in a patient an initial remission of metastasis in his lungs. This patient had stage IV lung cancer and metastatic prostate cancer, but he still had his prostate. On the basis of our experimental studies, we wondered whether the remission of these metastases had something to do with an immune response, which I subsequently characterized as cryoimmunotherapy.

We subsequently treated more patients by multiple cryotherapy of their prostates, and observed that several of these patients underwent remission of their metastases at distant sites. There was a lot of press and questions from the medical and lay communities about what was happening. Why is there an immune response? Is there is a tumor-specific or cancer-specific antigen? To answer that question, I started to look at the immunologic complexity, or the antigenicity, of the normal benign and malignant prostate. I hoped to find a cancer-specific antigen.

A Harbinger of Prostate Cancer Recurrence

Dr. Topol: Immunotherapy is one of the newest dimensions of cancer. That was your early work where you observed the PSA, but at that point did you think it was specific for cancer?

Dr. Ablin: To my dismay and disappointment, the tissue-specific antigen that I found -- PSA -- was the same protein found in the normal (benign) as well as the malignant prostate. It wasn't what I was looking for. We didn't have monoclonal antibodies in 1970, but with available techniques, we could see a spike in the area where PSA would have occurred, from a molecular standpoint. After treatment, if we followed this level, we saw a reduction of that peak. That was the forerunner of the test approved by the FDA in 1986 -- the PSA test that was the harbinger of the recurrence of the disease.

Dr. Topol: Yourbook reviews 40-plus years of the PSA test and what happened. One of the first things you discuss is how the PSA was commercialized by a San Diego company called Hybritech. This was the first company to manufacture a commercial PSA test. Was that commercialization of the PSA ill-founded?

Dr. Ablin: The difficulty is that the 1986 approval by the FDA was to use the protein as a harbinger of the recurrence of the disease, and that is what it is used for today. This is a very important observation. Because of the tissue specificity of the protein, it allows us to follow a patient after treatment. When you remove the prostate, for example, you remove the source of the protein.

Dr. Topol: That is a legitimate use of the PSA -- to track the prostate gland after surgery. So you didn't have a problem with the commercialization or initial FDA approval?

Dr. Ablin: One problem with the FDA approval was that when Paul Lange presented data to the advisory committee meeting in 1985, Hybritech was really after detection. They had in mind developing some sort of blockbuster drug or form of immunotherapy. There was some disappointment on their part when they went to the FDA, because they didn't have prospective data. They had only retrospective data, and a lot of questions were raised. They didn't get what they wanted to get in 1986.

The Calamity of Mass Off-Label PSA Screening

Dr. Topol: In 1994 (8 years later), the FDA approved the PSA test for routine use in men aged 50 years and older. That is what the company was initially after. What created the big problem?

Dr. Ablin: The calamity was that right after its approval in 1986, people started to use the PSA test off-label. The only company that was permitted to produce the test kit was Hybritech, but several other biotech companies began producing it shortly after the approval. A tsunami began in the urology community when clinicians started to use the PSA test off-label between 1986 and 1994. This was a crime, because they were using a test that was approved as a harbinger of the recurrence of the disease for the detection of prostate cancer 8 years before it was approved for that indication.

Furthermore, it should have never been approved for that purpose, because at the advisory committee hearing in 1993 (before the 1994 approval), many members of the committee opposed it. For example, Alexander Baumgarten made the statement that because of the results that Bill Catalona was presenting, it was like Pontius Pilate; you won't be able to wash the blood (the guilt) off your hands because of the 78% false-positive rate.

How is a test with a 78% false-positive rate approved? Eric J. Topol, MD

Dr. Topol: How is a test with a 78% false-positive rate approved? As you wrote in the book, the PSA is wrong 80% of the time.

Dr. Ablin: Through the Freedom of Information Act, we obtained the transcripts of the 1985 and the 1993 meetings. A portion of the transcripts are reprinted in the book. The meeting had a circus atmosphere. Prostate cancer patient support groups were there. Lobbyists were there. Bill Catalona was saying that every few minutes, a man is dying of prostate cancer. The irony is that even Dr. Catalona said that the PSA test doesn't detect prostate cancer. It is a measure of risk. By his own admission, it wasn't a test for prostate cancer, but to determine the risk of developing prostate cancer. There was chaos.

We talked to some of the people who were present at the 1993 advisory board meeting and people from the prostate cancer advocacy groups. There was screaming and yelling: "Men are dying; you have to approve this test!" With the 78% false-positive rate, and being wrong 80% of the time, I don't know how the test was approved.

In the book, we also cover what it costs to go to the FDA. It costs a million dollars. Does that mean anything? I don't know. I can't say anything because I can't prove it, but something went on to lead to this approval.

Dr. Topol: Are you suggesting that there was a pay-off?

Dr. Ablin: How would they have approved a test with an 80% false-positive rate?

Fear and Money Keep PSA in Use

Dr. Topol: It seems outlandish, and you cover this in the book. We then go from 1994, when the FDA approves the PSA for mass screening, to today. I was presenting at the American Urological Association (AUA) in May 2013, the day after the professional society said that we should no longer use the PSA routinely.[2] Why did it go on for almost 20 years?

Dr. Ablin: Fear and money, because other than melanoma, prostate cancer is the most prominent cancer in men. It went on because of the continual proselytizing of fear and the money that was being generated by the screenings.

"Patients and doctors believe that lives have been saved by the PSA test. This is offset by all of the men who have developed urinary incontinence or who have lost sexual function -- all of the travesties that have occurred Eric J. Topol, MD

For example, in 1989, which was 5 years before the test was approved by the FDA for detection, Schering-Plough paid $1.2 million to a marketing firm during September, which is Prostate Cancer Awareness Month, to promote PSA screening. Primary care physicians were brainwashed that they needed to do a PSA test. If you don't do a PSA test and a man is subsequently diagnosed with prostate cancer, you could be sued.

Dr. Topol: Urologists who have incorporated the PSA test into their practice are still very tied to it , even after the May 2013 backing off from the AUA initial recommendations.[2] This happens because patients and doctors believe that lives have been saved by the PSA test. This is offset by all of the men who have developed urinary incontinence or who have lost sexual function -- all of the travesties that have occurred.

We know from the analyses that net benefit isn't there -- but there is striking net harm. In 2010, you wrote a *New York Times*[3] op-ed calling this is a public health disaster, and stating that several billion dollars a year could be saved by eliminating the PSA test as a screening test. That was back in 2010, and then you published this book. You said that you were working on it for several years. What were you trying to accomplish in the book?

As Costly as the Human Genome Project

Dr. Ablin: I will give you an example of why I call this a public health disaster, as you wrote in your book, *The Creative Destruction of Medicine* (Basic Books, 2013).[4] Our healthcare system is broken. The latest statistics show that the annual budget for the National Cancer Institute is about $5.1 billion; of that, approximately $300 million goes for urologic research. But every year, we spend $3 billion on PSA screening in asymptomatic men, using a test that can't do what it's purported to do.

Every year, we spend $3 billion on PSA screening … using a test that can't do what it's purported to do.
Richard J. Ablin, PhD

Dr. Topol: Even though the recommendations have changed by the US Preventive Services Task Force[5] and AUA,[2] there doesn't seem to be any decline in the use of PSA screening. Has it changed?

Dr. Ablin: Some reports have suggested a slight decrease. The other reason for calling this a public health disaster may hit closer to you because of your interest in genomics. The Human Genome Project, which took 13 years, also cost $3 billion, but look at all the information that we got out of the Human Genome Project. Just think: We spent $3 billion through Medicare and the

Veterans Administration in 1 year, not over 13 years, on PSA screening, using a test that can't do what it's purported to do.

Dr. Topol: And the cost is much larger than that, because of all the procedures that are done. You also discuss in the book that it is not just the fact that all of these biopsies, surgeries, and radiation treatments are being done, but use of the surgery has also led to such technologies as robotic surgery of the prostate, proton beams, and Dendreon immunotherapies. It developed this medicine-industrial complex. Do you want to elaborate on that?

Dr. Ablin: Robotic surgery is a train that is ready to come off the tracks. When the FDA approved robotic surgery for the prostate, the basis of that approval was cystectomy of pig bladders. There was never any study on the use of robotic prostatectomy.

Dr. Topol: There were no human data?

With the PSA test, we have tried to make a silk purse out of a sow's ear. It can't be done. Richard J. Ablin, PhD

Dr. Ablin: No. We are seeing the results now, which have been disastrous in many cases. The machine for robotic prostatectomy costs $2 million, with a $100,000 contract. Now we have proton-beam centers that cost $200 million. With the PSA test, we have tried to make a silk purse out of a sow's ear. It can't be done.

In the book, I talk about 4 cruxes that explain why the PSA test is not being used appropriately. First, the PSA test is not cancer-specific. Second, there is no cut-off, no dichotomy in the response for a certain PSA level. For many years, we used 4 ng/mL, but we now know that a man can have a PSA of 0.5 ng/mL and have cancer, or a PSA of 11 ng/mL and not have cancer.

Dr. Topol: Genomics can play into that. Some men are walking around with high PSA levels from a very young age.

Spawning an Industry for Drugs and Diapers

Dr. Ablin: Third, we can't tell the difference between latent cancer or nonclinical cancer and aggressive cancer. I make the analogy in the book of a rabbit and a turtle and an open box. The turtle crawls around the box and goes nowhere. That's the nonaggressive, indolent cancer. The rabbit, representing the aggressive cancer, can jump out of the box and metastasize anytime. The problem is, we can't tell the difference between a rabbit and a turtle.

The most important crux is that prostate cancer is an age-related disease. If you get, for example, 100 men -- black or white -- between the ages of 60 and 69 years and do biopsies, you will find that 65% of these men have prostate cancer because it's age-related.

Dr. Topol: But rarely is it aggressive. In the future, is it possible that we will identify a marker that will help sort out whether someone has an aggressive type of prostate cancer that warrants the big-gun treatments?

Dr. Ablin: Going back to when I started working on this in 1967, up to the present time, no one has found a cancer-specific antigen for the prostate. As we talk today, there are 11 -- and probably more -- tests out there that have been proposed as a replacement for the PSA. These tests are awaiting validation and clinical trials. I have reviewed these tests. So far, it's questionable as to whether any of them right now will fulfill what we are looking for.

Dr. Topol: They are not likely, at least imminently, to get us out of this bind of not being able to partition the serious types of prostate cancer from the innocent types. Is that right?

Dr. Ablin: One problem is that people are still using the PSA test. They go from PSA, to ultrasonography, to biopsy. It's a cash cow.

Book Reaction: Silence

Dr. Topol: Have you suffered any repercussions from the book? Have there been any lawsuits or any retaliatory-type tactics?

Dr. Ablin: No. In fact, there has been silence. Several articles have come out. I've had several interviews with the local papers.

Dr. Topol: You had a nice review in *The Economist*.[6] That's pretty widely read.

Dr. Ablin: That was the poorest review that we received, because it was anonymous, and whoever wrote it said that I made hyperbolic claims. Every single statement in this book is supported by a reference.

Dr. Topol: As you look back on the past 5 decades of PSA and what you have learned, do you think that it was a conspiracy, that it was intentional, or that it was unwittingly done trying to help men to try to prevent the sequelae of a horrible cancer? What do you really think?

I believe that the use of the PSA test for screening asymptomatic men was strictly for money -- a lot of money. Richard J. Ablin, PhD

Dr. Ablin: My opinion is that the driver of this, beyond the use of the PSA test as a harbinger of the recurrence of the disease, is money. There are some highly intelligent people in the industry. No one has ever refuted my 4 cruxes, so I believe that the use of the PSA test for screening asymptomatic men was strictly for money -- a lot of money. A company wanted to develop a blockbuster drug, some form of immunotherapy, which they talked about in the early days back in San Diego. Many people could see that this test couldn't do what it was purported to do.

I remember talking to a couple of CEOs at biotech companies a couple of years ago, and explaining to them why this test doesn't work. Their answer was, "Dick, this is very interesting, but nobody is going to be interested in your story." I asked why. They said, "Too many people are making too much money to stop this." This is why I wrote the book, and why it's so important that the average man and his family read it and have a better understanding of what's going on.

Dr. Topol: Thank you not only for writing the book, but for sharing your views. There is, obviously, another side to all this. I know we will hear from

our Medscape audience -- not just urologists, but primary care physicians -- about their views, and there will be a lot of disparity and even polarization of views about the PSA and screening for prostate cancer. Nevertheless, we are very appreciative to you for what you have done over these years, and for taking the time to join me on Medscape One-on-One.