The PSA Controversy: Details, Models, Analysis and Recommendations

The Telmarc Group, WHITE PAPER No 79

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ABSTRACT

PSA has been the standard marker for monitoring the potential for prostate cancer. There is a great deal of controversy regarding its use and effectiveness. There is an anticipation that with the new health care bill that there will be pressure to follow what has been called "watchful waiting" rather than treating the cancer. This is potentially a death sentence for a group of patients since some of the prostate cancers are highly virulent. In this paper we examine the PSA issue and in turn we look at the measures which are made and make suggestions regarding improving the treatment of patients. The literature on this topic is both vast and oftentimes contradictory. The introduction of comparative effectiveness research will undoubtedly add to the confusion and most likely morbidity and mortality. We believe that the analytical approach taken herein will assist in establishing an initial framework for dealing ethically and morally with patients. We further argue that it will take more complex genomic tests to have truly effective tools.

1 CONTENTS

1 INTRODUCTION

This paper deals with the use of one specific marker for prostate cancer. It looks at PSA and it develops quantitative methods and evaluates others which are useful in the application of PSA. There has been a great deal of confusion regarding this test as well as a great deal of misstatements on the part of many researchers. The recent publication of the of the American and European studies on the use of PSA and their conclusions that the monitoring of PSA did not affect any change in outcomes we believe is grossly in error. We make the argument herein that PSA is a useful tool albeit a limited one.

PSA is excreted by luminal cells in the prostate gland and is absorbed into the blood stream. The more such cells the higher the concentration of PSA and thus one could conceive, rightly so, that monitoring PSA is in effect monitoring the cells in the prostate. Exceptionally high growth of the prostate cells is often associated cancer. Thus PSA may be a harbinger of cancer and if it exceeds certain levels further studies should be performed. However PSA alone is not the sine qua non in this process. One must look at this in the context of the patient as a totality. The patient family history oftentimes trumps all since a first degree relative with an aggressive form of prostate cancer is more of a concern than just an elevated PSA. Prostate size in and of itself is a cause just because there are more cells. The change of PSA over time is also a significant factor. All too often the physician has little if any notion of that change. We believe that temporal factors of a patient are key to effective medical records, especially electronic medical records and this factor seem to play second seat to other administrative factors. The PSA velocity is a major factor ascertainable only by having the access to all records.

Finally and most importantly is the PSA assay itself. Measuring of PSA may vary by 25-50% from assay to assay. This is a clinical problem when seeking to ascertain such factors as PSA velocity.

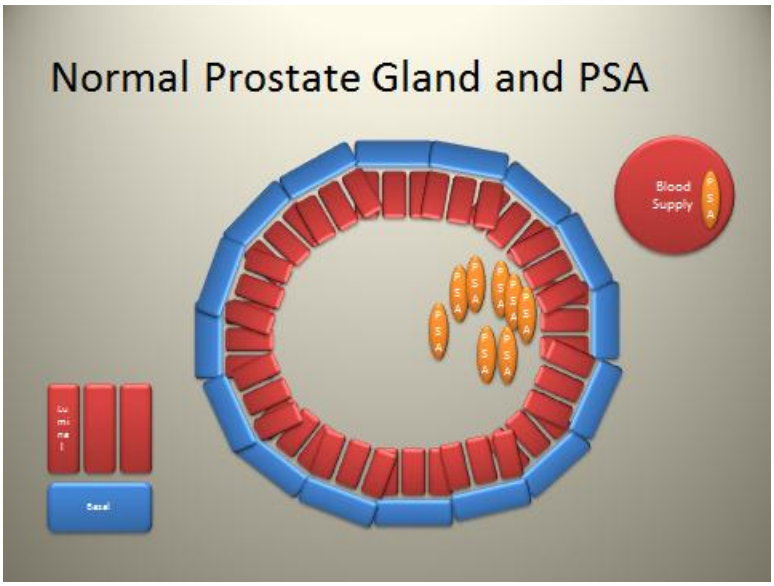
We will now look at PSA and its clinical use as well as looking at the methods and techniques by which various researchers have tried to reach the conclusions that they have. The work of Punglia and other have demonstrated, in 2003, that the thresholds for PSA tests vary dramatically from the young to the old. What has not been analyzed has been using PSA as a measure for ascertaining aggressive versus indolent prostate cancer, PCa. This has yet to be determined. We know the pathways but even using various stains to ascertain the presence or absence of certain proteins in the pathways has not evolved into a useful and predictable set of tests for aggressive types. That type of test will be the sine qua non for monitoring PCa.

2 PSA FUNCTION

Before detailing the cellular level of the pathology it is worth while discussing the PSA issue and the controversies related thereto.

The prostate is a 40 cc globe like gland just below the bladder and surrounding the urethra. It is composed of 35-50 glands and between the glands is a stroma composed of nerves, muscles, and blood supplies, with some other connective tissues. A typical gland is shown below along with an adjacent blood flow.

The following Figure graphically depicts the gland in the prostate and the PSA released mostly into the lumen of the gland but a small percent gets released into the blood supply.



PSA, prostate specific antigen, is a gene product of chromosome 19[1]. The PSA gene is androgen regulated. PSA is synthesized in the epithelial cells. It is secreted into the lumen of the prostate gland ducts and works its way into the serum most likely by diffusion. PSA tends to increase with hypertrophy and PCa. This most likely is due to cell proliferation and thus a larger base of excretion of PSA into the lumen. There does not however seem to be any studies relating serum PSA to prostate size, volume. A normal prostate is about 40 cc in volume and large prostates say of 60 cc may have more epithelial cells and thus putatively a larger PSA in the serum, however there does not appear to be evidence supporting this conjecture.

[1] See Kantoff, Prostate, p 213.

Most serum PSA is bound to proteins and there is some free. Thus the Percent Free PSA is often also measured. PSA released from cancer cells however is often not processed by intracellular proteolytic chains and thus is not free. High percent free is often a sign of no malignancy[2].

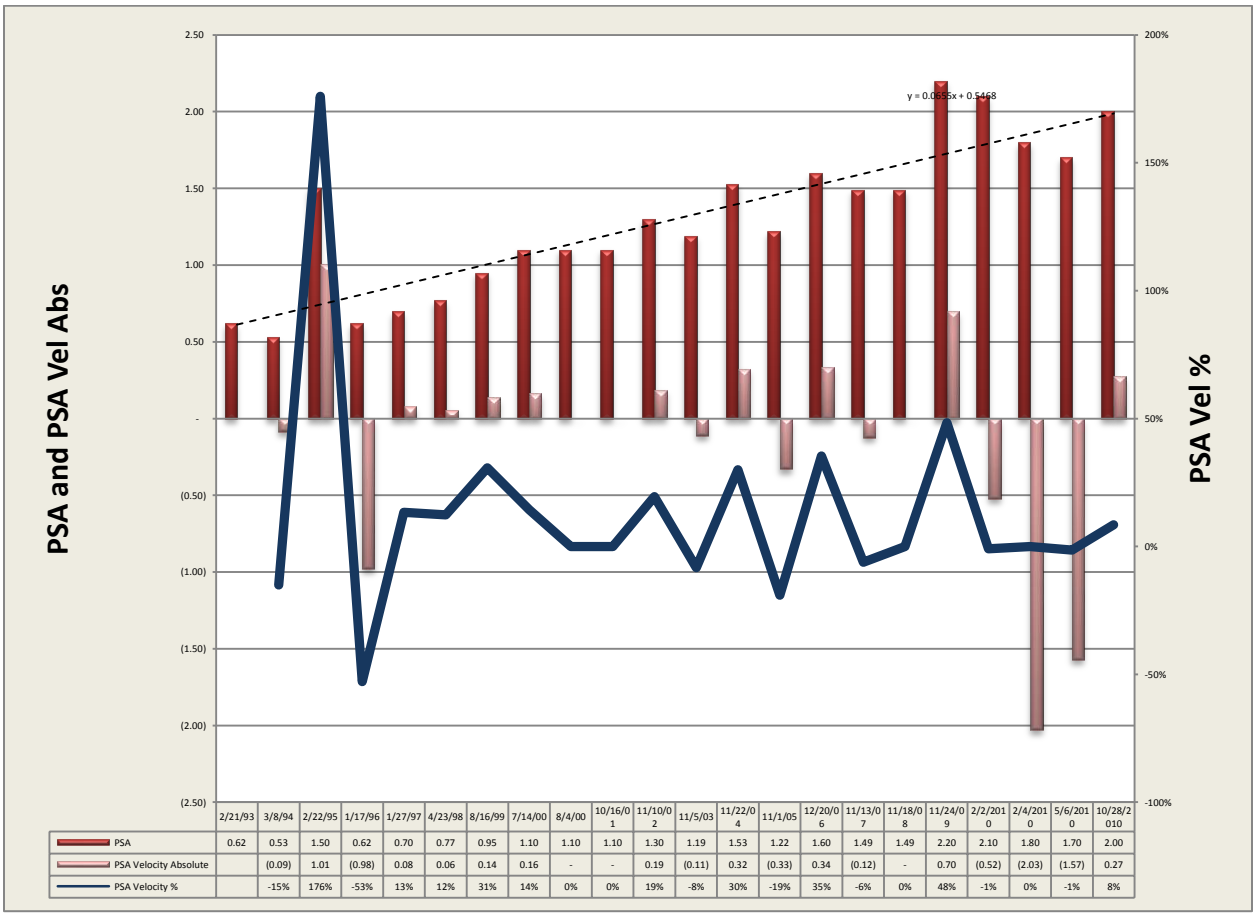
PSA velocity is another measure of malignancy potential. The definition of PSA velocity is the three sample average of PSA change per year or percent change per year. That is we take three time samples, and then calculate two velocities, from the second less first, and the third less second, and annualize each and take the average. If the velocity exceed 0.75 we have a threshold which requires examination[3].

2.1.1 PSA

We can now look at a typical PSA history. We show below a 20 year PSA history of a patient where we also show velocity as well as PSA change. The first problem we would have here is that there are most likely a dozen different assays so that any comparisons are difficult. Secondly we have a 20 year temporal change in assays as well so any consistent baseline is in question.

[2] Su, Prostate, p 5.

[3] Su, prostate. p 5.



	2/21/93	3/8/94	2/22/95	1/17/96	1/27/97	4/23/98	8/16/99	7/14/00	8/4/00	10/16/01	11/10/02	11/5/03	11/22/04	11/1/05	12/20/06	11/13/07	11/18/08	11/24/09	2/2/2010	2/4/2010	5/6/2010	10/28/2010
PSA	0.62	0.53	1.50	0.62	0.70	0.77	0.95	1.10	1.10	1.10	1.30	1.19	1.53	1.22	1.60	1.49	1.49	2.20	2.10	1.80	1.70	2.00
PSA Velocity Absolute		(0.09)	1.01	(0.98)	0.08	0.06	0.14	0.16	-	-	0.19	(0.11)	0.32	(0.33)	0.34	(0.12)	-	0.70	(0.52)	(2.03)	(1.57)	0.27
PSA Velocity %		-15%	176%	-53%	13%	12%	31%	14%	0%	0%	19%	-8%	30%	-19%	35%	-6%	0%	48%	-1%	0%	-1%	8%

Thus looking at the above we see a 4 fold increase in 20 years. This is for a male from 50-70 years of age. The change in the prostate during that period may be significant. It may grow in size and thus have increasing cells, it may have PIN, prostatic intraepithelial neoplasia, and also have more luminal cells, or it may have a low grade PCa. Thus looking at this patient one must ask what to do next? It will of course depend on family history more than the PSA changes.

2.1.2 PSA Velocity

In a paper by Carter et al the authors provide an excellent review and analysis of the use of PSA velocity. As the authors state, a driver for this study is:

Recently, D'Amico et al. showed that, when compared with men with a PSA velocity of 2.0 ng/mL per year or less in the year before diagnosis, men with a PSA velocity above 2.0 ng/mL per year were at an increased risk of prostate cancer death after surgical treatment. An unanswered question is whether a lower PSA velocity could identify those men with life-threatening prostate cancer during a window of curability.

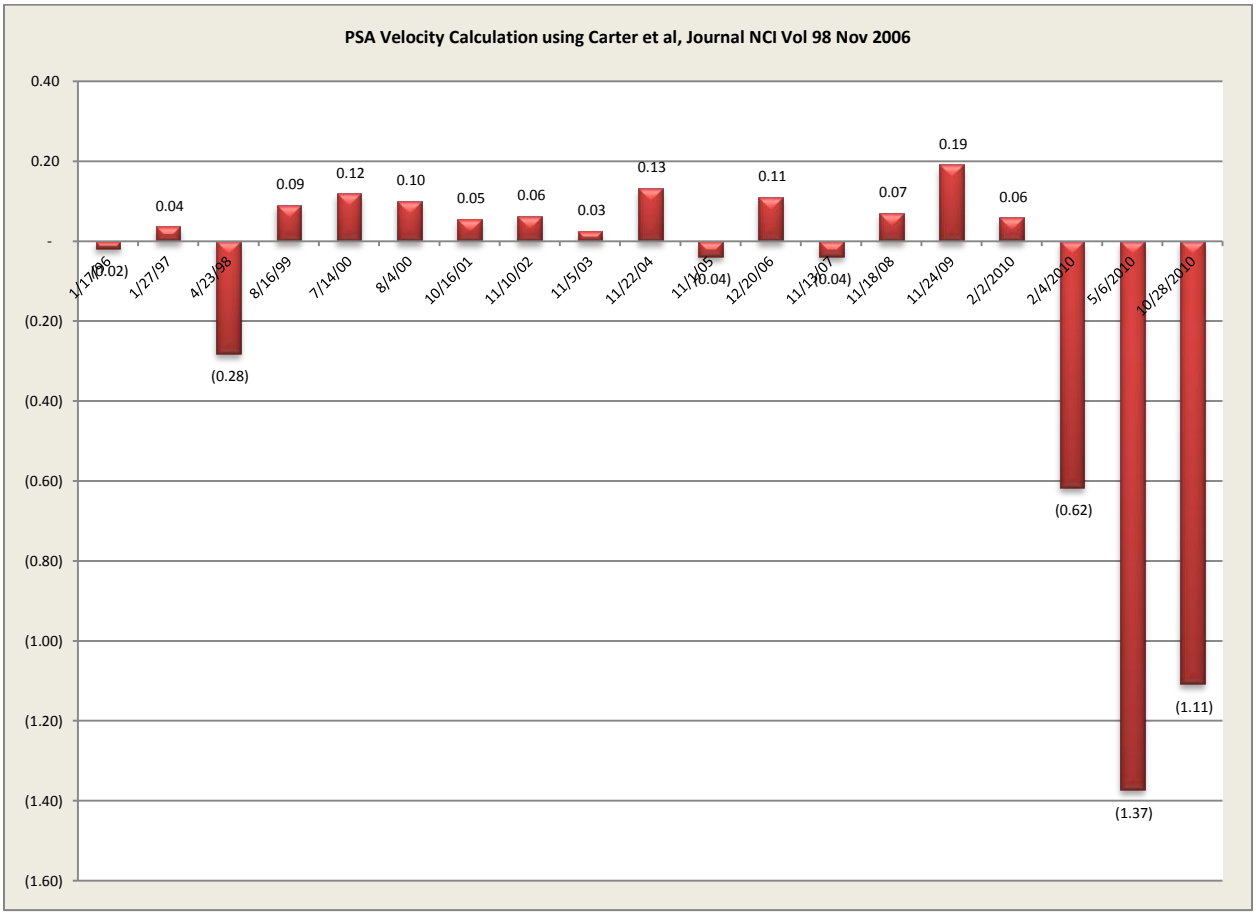
This PSA velocity is a significant factor. As defined by Carter et al:

PSA velocity in ng/mL per year was calculated for each subject (n = 788) as the running average of the rate of change over three consecutive visits (the index visit and the two preceding visits), when more than two PSA measurements were available (5) , or as the simple rate of change, if only two measurements were available.

Or we can use the following:

$$V_{PSA}(k) = \frac{\sum_{n=k-3}^{k} \frac{PSA(n) - PSA(n-1)}{Date(n) - Date(n-1)}}{3}$$

We have used this formula on the data above and have shown the velocity where we use units in years. The negative values are driven by a single poor PSA reading. One must be careful in performing this analysis to include consistent assays. That is often the problem.



The results by Carter et al are:

PSA velocity measured 10 – 15 years before diagnosis (when most men had PSA levels below 4.0 ng/mL) was associated with cancer specific survival 25 years later;

survival was 92% (95% confidence interval [CI] = 84% to 96%) among men with PSA velocity of 0.35 ng/mL per year or less

and 54% (95% CI = 15% to 82%) among men with PSA velocity above 0.35 ng/mL per year (P <.001).

Furthermore, men with PSA velocity above 0.35 ng/mL per year had a higher relative risk of prostate cancer death than men with PSA velocity of 0.35 ng/mL per year or less (RR = 4.7, 95% CI = 1.3 to 16.5; P = .02);

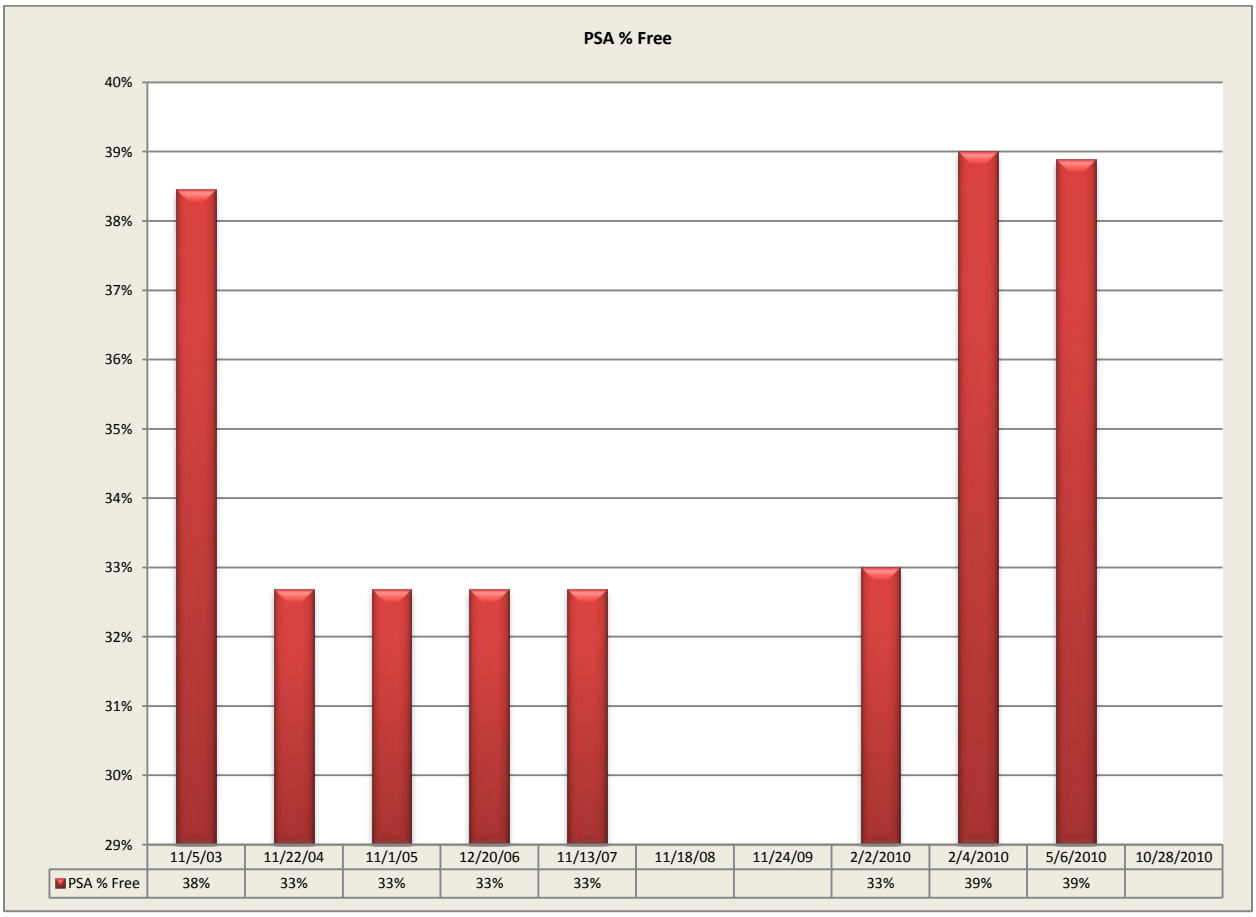
the rates per 100 000 person-years were 1240 for men with a PSA velocity above 0.35 ng/mL per year and 140 for men with a PSA velocity of 0.35 ng/mL per year or less.

Thus in looking at the above patient we should conclude with Carter that even if PCa is discovered it should have a reasonably good chance of survival. Yet again the issue is always one of assay consistency.

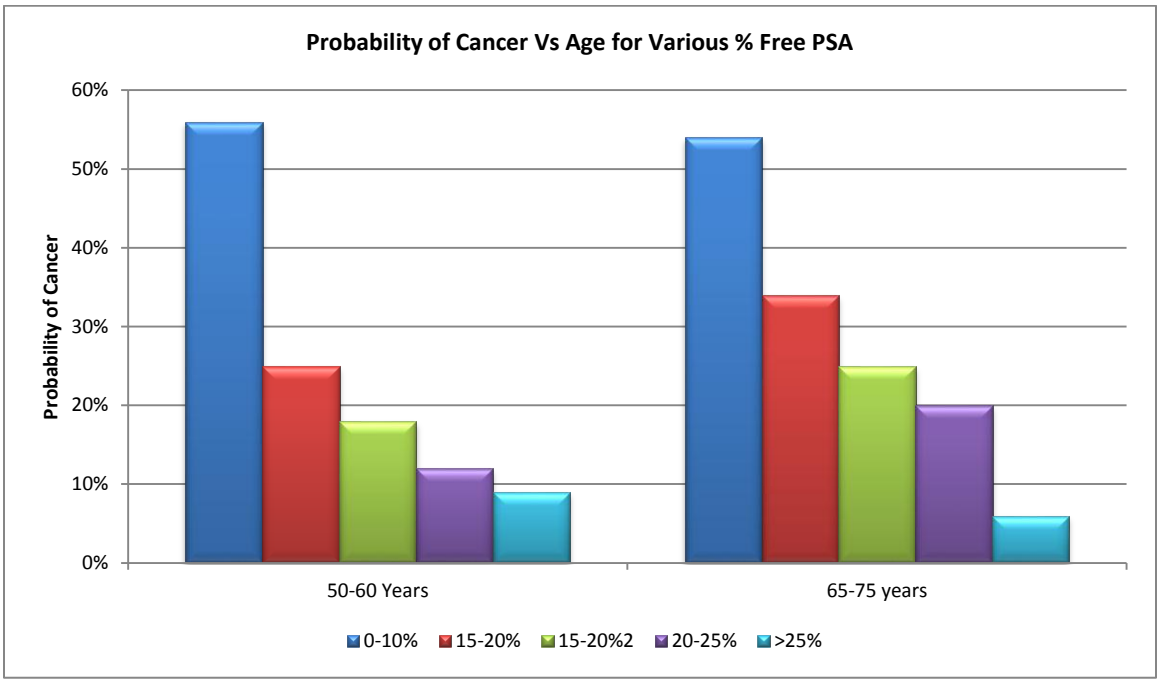
2.1.3 Percent Free PSA

The percent free PSA is a measure of the PSA generated by benign luminal cells which is unbound to proteins in the circulation. The majority of PSA in the blood stream is bound to proteins, primarily α-antichymotrypsin. The remaining amount, from about 5% to 35%, is free. PSA released from cancer cells is generally bound and not free. Thus the increase in PSA with a concomitant reduction in percent free is an implication of PCa. On the other hand, if PSA slightly rises and free PSA also rises, or stays at peak, then one would suspect a benign process of hyperplasia or benign or non-malignant neoplasia. As we progress to PCa, the luminal cells which are malignant clones do not have free PSA and thus the percent free drops.

In the case of the patient we have been examining we see a percent free in excess of 39% which appears to indicate no malignancy.



This the above Percent Free PSA appears to be benign. Again we also must note the change in values may be driven more by the assay than any underlying process. The chart below is modified from Yang and the data taken from Catalona et al. It shows that the higher the percent free the lower the risk of cancer.



2.2 The PSA Controversy

The use of PSA has become quite controversial over the past few years and especially as the new health care laws have been mandated by the Democratic Congress. The main putative issue is the subsequent biopsies required and their costs as well as the resulting prostatectomies and their morbidities as well as costs, given the putative prevalence of indolent PCa. Namely there are groups who argue that PCa is generally a benign factor and that with death as an end point, the actions resulting from PSA measurements are often lacking in changing the end point, namely men die at the same rate whether treated or not.

Professor Ablin, the researcher who discovered the PSA antigen which is used in testing for prostate cancer, PCa, wrote a scathing editorial in the NY Times this decrying the test and its implications[4]. He starts by stating:

The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with — I discovered P.S.A. in 1970. As Congress searches for ways to cut costs in our health care system, a significant savings could come from changing the way the antigen is used to screen for prostate cancer.

[4] http://www.nytimes.com/2010/03/10/opinion/10Ablin.html

Americans spend an enormous amount testing for prostate cancer. The annual bill for P.S.A. screening is at least $3 billion, with much of it paid for by Medicare and the Veterans Administration.

There is significant disagreement here. That the PSA test alone has some problems, which is well recognized. Yet this test alone, as a single measurement upon which to act dramatically, was never intended to be used that way. Thus the whole basis for his argument lacks any substantial merit. I will make my argument as follows.

1. PSA by itself as a onetime test with a threshold of 4.0 as applied to all men does not significantly reduce mortality. This is a true fact. The Professor states:

The medical community is slowly turning against P.S.A. screening. Last year, The New England Journal of Medicine published results from the two largest studies of the screening procedure, one in Europe and one in the United States. The results from the American study show that over a period of 7 to 10 years, screening did not reduce the death rate in men 55 and over.

The European study showed a small decline in death rates, but also found that 48 men would need to be treated to save one life. That's 47 men who, in all likelihood, can no longer function sexually or stay out of the bathroom for long.

As we will demonstrate, these studies used the 4.0 level as the benchmark and the European study had long periods between testing and the US study did two year testing and again applied 4.0 for all.

None of the studies recognized the newer research that said that 2.0 was the threshold for those under 60 and that velocity was a major component to be added. Velocity, the averaged change in PSA per year, is recognized as a major factor and that if the velocity exceeds 0.75 per year for men over 65 and with a stable PSA over 4.0 then the sensitivity and specificity rises appreciably. Second for men under 60 or with a baseline long term PSA under 2.0, if the velocity exceeds 0.25 the sensitivity and specificity also is quite high.

Also we know that free PSA and % Free PSA are further indicators of PCa, since the PCa cells bind the free PSA whereas the normal acinar cells do not.

Finally, family history is critical. It falls into three categories; no PCa, PCa of an indolent form, and PCa of a virulent form.

Thus if one has no PCa in one's family then most likely you have a lesser chance of having a virulent PCa. If your family history is of indolent forms then there is a good chance you too with have that form. If your family history is of a virulent form then you

too may most likely have that form. What is a virulent form, well my father had that form. PSA went from 4 to 40 in two years and 40 to death in two years! Why did that happen, well we do not yet fully know the dynamics of the cancer pathways, we do know that PTEN and its pathway were knocked out at some point and off it went.

Using a Bayes methodology, we really want to measure the following probability:

P[PCa| PSA, PSA Velocity, Percent Free, Percent Free Velocity, Family History]

Then given the a priori data we can determine an a posteriori probability and act accordingly.

Professor Albin appears to neglect all of these facts. Albin continues his exhortation:

So why is it still used? Because drug companies continue peddling the tests and advocacy groups push "prostate cancer awareness" by encouraging men to get screened. Shamefully, the American Urological Association still recommends screening, while the National Cancer Institute is vague on the issue, stating that the evidence is unclear.

The federal panel empowered to evaluate cancer screening tests, the Preventive Services Task Force, recently recommended against P.S.A. screening for men aged 75 or older. But the group has still not made a recommendation either way for younger men.

Prostate-specific antigen testing does have a place. After treatment for prostate cancer, for instance, a rapidly rising score indicates a return of the disease. And men with a family history of prostate cancer should probably get tested regularly. If their score starts skyrocketing, it could mean cancer.

The test, when combined with other variables has been shown to have merit. Yet one of the factors is the patients history, the long term PSA data, not a single PSA measurement. One of the problems with a single PSA measurement is that there is a +/- 50% variation in PSA measurements. The PSA may vary from say 1.5 to 1.8 to 2.1, to 2.1 in the same person but using differing assays. That in itself would set off alarms. Yet, if there were a 20 year history then one could better determine the velocity and watch for results and not jump to surgery. Albin seems to reject the volume of clinical data with his position. Yet Albin's position is all too common and one wonders why.

One can also look at more Facts. For example, prostate biopsies, using the classic sextant or 6 core forms, have been notoriously poor in detecting cancer. In addition the biopsy cannot as current performed determine indolent versus virulent forms, that is a genetic marker issue. One could do an assay on the cells for PTEN marker presence but that is still an experimental procedure. One could use the PCA3 test which determines Gleason 7 or greater with reasonable specificity and sensitivity but that is only a recent

development and by the time one gets to Gleason 7 one may have a PCa which will have positive margins after prostatectomy.

One would like to get PCa at Gleason 5 or 6 with negative margins. This often means more cores. Thus for say a 40 cc prostate one needs 12 to 14 cores, and yet one may still have a 20% or greater chance of missing a cancer. In a larger prostate, say 60 cc one may need 20 cores and yet still have an almost 20% chance of detecting a PCa on the next biopsy say 6 months later.
The problem is that we do not have the genetic tools to detect PCa, and in fact almost all Cancers, at the earliest a stage. The problem with PCa is that we do not know the indolent from the virulent from even at biopsy.

Is the answer as Albin argues seems to be to just abandon the testing. Death from PCa is not a pretty picture, it is akin to breast cancer, especially with mets to the bone. Mets to bones, collapse of the spine, result in disseminated intravascular coagulation, and is not a pretty picture.

The House Oversight Committee has held hearings on prostate cancer and testing and their intent seems to influence CMS to reduce the screening[5]. The American Cancer Society issued new guidelines for screening and they seem to retain PSA screening[6]. NIH recounts the ACS guidelines as follows[7]:

In new guidelines released … the society (the ACS)says that men who choose to be tested should get an annual screening if their level of prostate-specific antigen, or PSA, is 2.5 nanograms per milliliter (ng/mL) or higher. But men whose PSA is under that threshold can be safely screened every two years. Men with a PSA level of 4.0 ng/mL or higher should consider getting further evaluation, such as a biopsy. Previous guidelines had suggested that men with a PSA of less than 4.0 ng/mL should be screened annually.

While the cancer society does not recommend screening for anyone -- even men at risk -- it does offer suggested intervals for screening if men choose to be tested.

The ACS specifically states:

[5] http://oversight.house.gov/index.php?option=com_jcalpro&Itemid=1&extmode=view&extid=126

[6] http://caonline.amcancersoc.org/cgi/content/full/caac.20066v1

[7] http://www.nlm.nih.gov/medlineplus/news/fullstory_103229.html

Studies are being done to try to figure out if early detection tests for prostate cancer in large groups of men will lower the prostate cancer death rate. The most recent results from 2 large studies were conflicting, and didn't offer clear answers.

Early results from a study done in the United States found that annual screening with PSA and DRE did detect more prostate cancers, but this screening did not lower the death rate from prostate cancer. A European study did find a lower risk of death from prostate cancer with PSA screening (done about once every 4 years), but the researchers estimated that about 1,400 men would need to be screened (and 48 treated) in order to prevent one death from prostate cancer. Neither of these studies has shown that PSA screening helps men live longer (lowered the overall death rate).

The statement is wrong about the two studies released in 2009 and we will detail the analysis later in this paper. However to summarize our objections to the two studies, they both used the 4.0 PSA level and the testing was sporadic at best, failing to do annual tests, lacking % Free PSA data, and especially failing in any meaningful measurement of PSA velocity. The answer is that mortality will most likely not change if one waits until a 4.0 is reached in many sub-groups. The set point was reduced to 2.0 in the Punglia et al work we discuss herein as data was obtained but the trial never tested the lower level thus by leaving it at 4.0 they allowed the cancers to grow to a terminal stage.

They continue:

Prostate cancer tends to be a slow growing cancer, so the effects of screening in these studies may become clearer in the coming years. Both of these studies are being continued to see if longer follow-up will give clearer results.

This is also in error. Prostate cancer falls in two categories; slow growing or indolent and this represents about 90% of all such cancers and fast growing deadly type which kills in 4 years or less. The recommendation of the ACS could be a death verdict for the men in the latter category. The problem is that we do not know genetically how to determine this category.

For example, we now know that two factors, percent free PSA and PSA velocity are major factors and not just PSA. Percent free is a measure of the percent of cells which are functioning normally, albeit they may be PIN cells, prostatic intraepithelial neoplasia, high grade, HGPIN, which may be a precursor to prostate cancer. HG PIN must be monitored by biopsy on a schedule of three to four times a year! Not ignored. Velocity is critical since it is a reasonable measure for the growth of cells. Also a measure for both PIN and prostate cancer.

We know that even a biopsy can at best be 10-25% in error. A 20 core biopsy can still miss cancer with a 10% probability. In addition a second biopsy using 14 or more cores may find cancer 25% of the time or more on a second testing!

The aggressive prostate cancer can kill a man in less than 4 years! Do we want that risk? If you are in that group I would think not. What further helps, family history. If you have had a first degree relative who died in a short period then it is highly likely that you have inherited the genetic errors that allow rapid growth, namely the elimination of the PTEN gene and thus metastasis.

The ACS also states:

Because of these complex issues, the American Cancer Society recommends that doctors more heavily involve patients in the decision of whether to get screened for prostate cancer. To that end, ACS's revised guidelines recommend that men use decision-making tools to help them make an informed choice about testing. The guidelines also identify the type of information that should be given to men to help them make this decision.

The problem is how do you involve a man if the physician has no understanding and in fact is confused given the literature. Biopsy is not a gold standard, it may be a silver or bronze. If the biopsy yields a Gleason 6, rarely less since most pathologists will grade 3+3 yielding Gleason 6, and almost never grade a 1 nor even a 2, then one still does not know the genetic makeup, the true determinant. In fact most physicians do not understand the genetic factors, including many urologists. Thus in many ways it is the blind leading the blind, and the ACS has done nothing more than put stumbling blocks in the way. Further by testifying before Congress they have done men a disservice. Yet it does reduce Medicare costs, we just let those old folks die, and yes many young ones two.

2.3 The Conflict in PSA Studies

In a recent Urology Today posting they discuss the variations in PSA testing and PCa, prostate cancer, in Europe and the US[8].

Specifically they state:

This study compared PSA screening performance for detecting CaP in the ERSPC-Rotterdam with the US population. The authors report that PSA screening performance in this analysis could provide quantitative explanations for the different mortality results

8 http://www.urotoday.com/61/browse_categories/prostate_cancer/editorial__prostatespecific_antigen_screening_in_the_united_states_vs_in_the_european_randomized_study_of_screening_for_prostate_cancerrotterdam03112010.html

of ERSPC-Rotterdam and the US Prostate, Lung, Colorectal and Ovarian trial. ..The model includes 18 detectable preclinical states in the natural history of CaP that are derived from combinations of clinical stage, grade, and metastatic stage. In this model, PSA testing and subsequent biopsy is modeled as a single test, therefore PSA test sensitivity also depends on whether a positive test is followed by a biopsy.

...The predicted CaP incidence peak in the US was higher than the observed CaP incidence Peak (13.3 vs. 8.1 cases per 1,000 man-years), suggesting a lower detection of CaP in the US than in ERSPC-Rotterdam. The lower sensitivity of PSA screening in the US compared with ERSPC-Rotterdam may be due to a higher PSA cutoff level for recommending biopsies in the US. Data suggests that the biopsy compliance rate is over twice as high in the screening arm of ERSPC-Rotterdam. However, other differences included racial differences between the US and Rotterdam, frequency of PSA testing, explanations for the drop in CaP incidence after 1992 and the inability to compute 95% confidence intervals for the sensitivity parameters.

The study found that PSA screening in the US did not detects as many CaPs as in ERSPC-Rotterdam due to the lower sensitivity of PSA testing followed by a biopsy.

This study presents in a bit convolved way the problems with PSA testing. They are:

1. PSA tests are not consistent. One assay will give different results from another assay. The difference that we have measured can be as great as a 50% variation from assay to assay. The stated variation is less than 10% but the measured is closer to 50%. Thus a single test can have great variability.

2. Repeat testing with the same assay also has testing variances due to life style. Namely irritated prostates and the like cause variations in PSA as much as 25%.

3. PSA Velocity, VPSA, is the dominant test metric and that requires many years of tracking. It is the average of three consecutive measurements and the derivation of velocity therefrom. Thus one needs a good baseline of ten years of annual PSA data at a minimum to determine reliable PSA velocity. The three sample test is an attempt to reduce the variability from the above two causes.

4. There is a recent tendency to delay biopsy from an exaggerated PSA test. In fact many internists and family physicians do not pay attention to velocity because they do not have access to the data! It is questionable if they are even aware of the velocity testing.

5. The problem today is that PSA testing looks at just one PSA sample and we know they are highly variable. Thus rather than sampling bi-annually the test should be performed annually and the long term data recorded and analyzed.

The problem of having data on patient histories is pandemic. For example the PSA is but one yet so too is HbA1c, and even blood pressure as well as HDL and many other variables. Medicine is a science and art which is often driven by a change, change in some chemistry measurement, change in weight, sight, moles, and the like. Thus it is imperative that a good HIT notwithstanding that the patient develop their own records, and bring them with them to the physician. Noticing a change can save a life.

2.4 PSA and Comparative Effectiveness Research

We have argued elsewhere against CER in the new health care bill. Our argument is that CER as so structured takes away from the open clinical field the results and codifies them in a Government panel and uses the hammer of reimbursement as the motivator for employing the new mandates. In NEJM there was a recent article describing the next steps that are to be taken with CER. They state them as follows[9]:

Institute of Medicine's Recommendations for a National System of Comparative-Effectiveness Research (CER).

1. Prioritization of CER topics should be a sustained and continuous process, recognizing the dynamic state of disease, interventions, and public concern.

2. Public participation (including participation by consumers, patients, and caregivers) in the priority-setting process is imperative for ensuring that the process is transparent and that the public has input into the delineation of research questions.

3. Consideration of CER topics requires the development of robust, consistent topic briefs providing background information, an understanding of current practice, and assessment of the research status of the condition and relevant interventions.

4. Regular reporting of the activities and recommendations of the prioritizing body is necessary for evaluating the portfolio's distribution, its effect on discovery, and its translation into clinical care in order to provide a process for continuous quality improvement.

5. The secretary of HHS [Health and Human Services] should establish a mechanism — such as a coordinating advisory body — with the mandate to strategize, organize, monitor, evaluate, and report on the implementation and impact of the CER program.

[9] http://healthpolicyandreform.nejm.org/?p=3017&query=home

6. The CER program should fully involve consumers, patients, and caregivers in key aspects of CER, including strategic planning, priority setting, research-proposal development, peer review, and dissemination.

7. The CER program should devote sufficient resources to research and innovation in CER methods, including the development of methodologic guidance for CER study design — for instance, on the appropriate use of observational data and approaches to designing more informative, practical, and efficient clinical trials.

8. The CER program should help to develop large-scale clinical and administrative data networks to facilitate better use of data and more efficient ways of collecting new data to inform CER.

9. The CER program should develop and support the workforce for CER to ensure that the country has the capacity to carry out the CER mission.

10. The CER program should promote rapid adoption of recommendations based on CER findings and conduct research to identify the most effective strategies for disseminating new and existing CER findings to health care professionals, consumers, patients, and caregivers and for helping them to implement changes based on these results in daily clinical practice.

The analysis of these objectives leads to further insight as to where these folks are going. To reiterate, CER, as best as I understand their meaning, albeit inferentially, since one cannot find a delimited definition, it is expansively defined by what it does, a typical Government program, is a Government program targeting clinical studies, with the participation of a broad based of interested parties, who will in some undefined manner develop and recommend, perhaps mandate, clinical procedures related to the delivery of health care to Americans.

Frankly this is the antithesis of how medicine or any science is practiced. Imagine is we have had such a group in physics, chemistry, engineering, a centralized Government entity telling us what the problems are that we should consider and then seeking the input from many third party interest groups who may totally lacking in any expertise and then setting up what the truth is. Would we have an Einstein, a Schrodinger, a Feynman, a Wiener, or perhaps a Banting or Osler, where would those ideas come from that were initially non-conformists? Frankly are these people just plain Orwellian!

The authors, clear supporters of this plan, state:

First, the national CER program must develop an overall funding strategy. It could follow the traditional biomedical research model by inviting proposals on any of the 100 high-priority topics and awarding grants to the scientifically strongest proposals. However, the

research interests of individual investigators would then define the national priorities. Instead, we believe that the national CER program should decide on a coordinated portfolio consisting of research on priority topics, infrastructure enhancement, and studies of translation and adoption.

Medical research has been around for over a century and it continues to evolve as we learn more. It is iterative and it modifies itself as we learn more. Some studies are well posed at their initiation but flawed by the time they are completed. I come back to the classic prostate cancer studies. They were started when a PSA of 4.0 was considered the gold standard. Over the years we have found that a PSA of 2.0 is as important for a younger man as 4.0 is for an older and also that PSA velocity is more a predictor. It is iterative and in some ways combative. A national CER program is consensus driven, worst of all worlds.

Second, the CER program should establish an initial list of priority topics and evaluate the current state of knowledge about each. For the first of these tasks, it should build on the priority-setting work of the IOM committee. It could develop a portfolio chosen from the top 25 IOM topics by applying the already-published prioritization criteria of the IOM

The portfolio is already there as a matter of ongoing research. Why redo the effort? Is this nothing more than justification for billions of more dollars spent by the Government. The money is spent well now why do we need change.

Third, the CER program, with the help of expert advisory committees and the research community, should choose the research methods that will fill gaps in the evidence for a specific topic. In an investigator-initiated research program, the grant applicant typically chooses the methods. The cost of studies using the methods of CER (whether clinical trial, observational study, or qualitative research) varies widely.

Evidence is always changing. Back to my prostate example. We know also that 5-10% of prostate cancers are highly aggressive. The question is why? Perhaps the four or five gene hits, ultimately knocking out PTEN, leads to the aggressiveness. Perhaps many men have genetically had the hits and they are predisposed, possibly there are epigenetic factors as well. These are the issues we should be working on, and these are the issues which the highly motivated and competent researchers are already working on. Why do we need another group? That question has never been answered. Perhaps to create approved methods to just "kill of the old folks" and replace the "death panels" with "death procedures".

Fourth, the program should strive for a balanced portfolio of high-impact research topics. Although it could simply rank topics in order of importance and fund them in ranked order until the money ran out, we recommend developing a portfolio that addresses a balanced distribution of topics, outcomes, and target populations, as well as

keeping the total portfolio cost within budget and producing a body of evidence sufficient to influence health care decisions.

The nature of the portfolio changes as we learn more each step. Dynamic portfolios are common in the way we do research now. The "hot topic" appears and researchers follow the path. Having a bunch of Government chart preparers do this is frankly insane!

Fifth, the CER program should evaluate progress and report to the public. To meet this obligation, it should do large-scale, ongoing observational research and evaluation to measure CER's effects on clinical practices and patient outcomes.

This I really do not understand. Medical research is always publicly available, NEJM is on line, as is JAMA and the list continues. Clinical trials are an everyday affair, just read NEJM and JAMA and the hundreds of other journals. So what is the point? Just spending more money.

The only possible reason for CER is Government control. Control over what the Government will pay for and worse the control over what physicians can do. This is not the code of civil procedure used in Federal Courts, this is science, and as such changes. Having the Government as the regulator of change is not just stupid it is immoral.

The British Journal of Cancer has just published an interesting article regarding Prostate Cancer[10]. They state:

There is evidence that prostate cancer (PC) screening with prostate-specific antigen (PSA) serum test decreases PC mortality, but screening has adverse effects, such as a high false-positive (FP) rate. We investigated the proportion of FPs in a population-based randomized screening trial in Finland...An FP result is a common adverse effect of PC screening and affects at least every eighth man screened repeatedly, even when using a relatively high cutoff level. False-positive men constitute a special group that receives unnecessary interventions but may harbor missed cancers. New strategies are needed for risk stratification in PC screening to minimize the proportion of FP men.

The last statement is the most powerful. It states that despite the false positive, namely a man is told that an increased PSA may be an indicator for Prostate Cancer, and then after a biopsy there does not appear to be any, then shortly thereafter they do come down with PCa. Namely false positives may not truly be false positives but early true positives. Specifically the histological test of looking at cells may not be the correct early assessment method.

[10] http://www.nature.com/bjc/journal/v102/n3/abs/6605512a.html

The Cancer Research UK states in their assessment of the article the following[11]:

The study, a clinical trial of the controversial PSA test for prostate cancer, tells us that false-positives are common. It also shows that men who get a false alarm:

1. *are likely to get another one the next time they go for a PSA test*
2. *are likely to refuse future invitations to screening, and*
3. *are likely to actually be diagnosed with prostate cancer the next time round*

The third result, in particular, is a fascinating one. It suggests that men who get a false-positive result through PSA testing, in the words of the researchers, "constitute a special group". They could well go through unwarranted tests, but they could also harbor missed cancers that only turn up later.... As we mentioned above, there's a large prostate screening trial running across Europe, called ESPRC. The new results, published in the British Journal of Cancer, (which Cancer Research UK owns) come from the Finnish part of this trial – its largest component.
It involves more than 80,000 men, some of whom were randomly invited to three rounds of PSA testing, with four-year gaps between each round. Roughly 30,000 men attended their first round of screening and more than 10,000 of these men went on to attend all three rounds.

The study showed that false-positives are a common part of PSA testing. In any individual round of testing, the majority of positive results are false alarms (between 60 and 70 per cent), while just over a quarter lead to an actual cancer diagnosis. Among the men who attended at least one round of screening, 1 in 8 had at least one false-positive result.

It's worth noting that the researchers were using a fairly high cut-off level of PSA (4 ng/ml) – i.e. the level above which they were thought to have suspected prostate cancer. This sets a pretty high bar for a positive result and should minimize the number of false positives. Nonetheless, many still crept through.

Among the men who get a false alarm in one round, more than half will get another false alarm in the next one. Many men without tumors have persistently high PSA levels for some other reason, so they keep on testing positive. That's a lot of extra worry and more potential for unneeded tests.

[11] http://scienceblog.cancerresearchuk.org/2010/01/20/the-meaning-of-false-alarms-in-prostate-screening/

Indeed, in this trial, every third man who got a false alarm went through two biopsies within 4 years of their result. That's probably an underestimate too, as it doesn't account for any visits to private doctors.

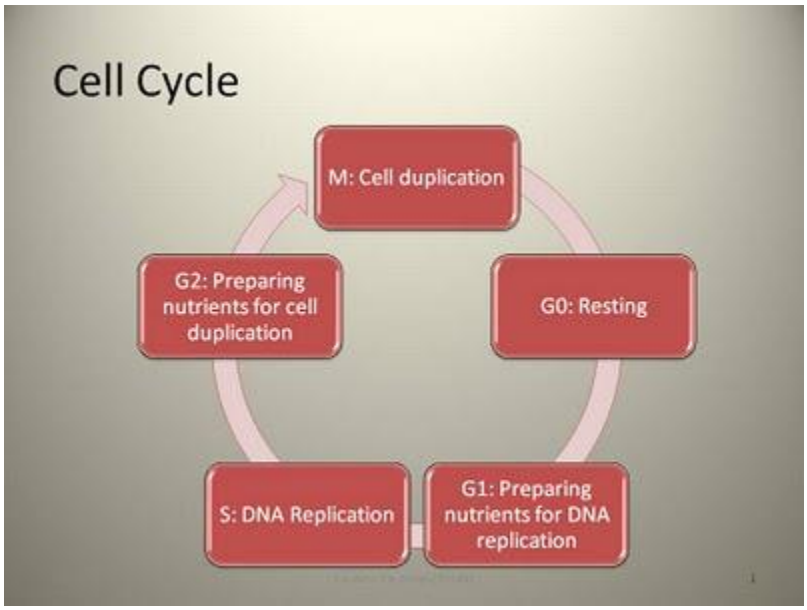
However, the study also shows that false-positives aren't entirely meaningless. If men had a false alarm during one round of screening, they were 3-9 times more likely to be diagnosed with prostate cancer during the next round...."

The analysis of the poor trials mentioned above is what we had commented on a year ago when the results were issued. Namely they used the 4.0 PSA level which we now know to be wrong, especially for men under 65. In addition we also now know that the better measure is PSA velocity, namely the change in PSA in a year's time. If the change is 0.75 or greater then there is a 90% chance of Prostate Cancer. That is a fairly good metric. Thus is you have a PSA of 1.5 in one year and the next year it is 2,25, you have a 90% chance of incipient PC.

3 BASIC PROSTATE CANCER GENETICS

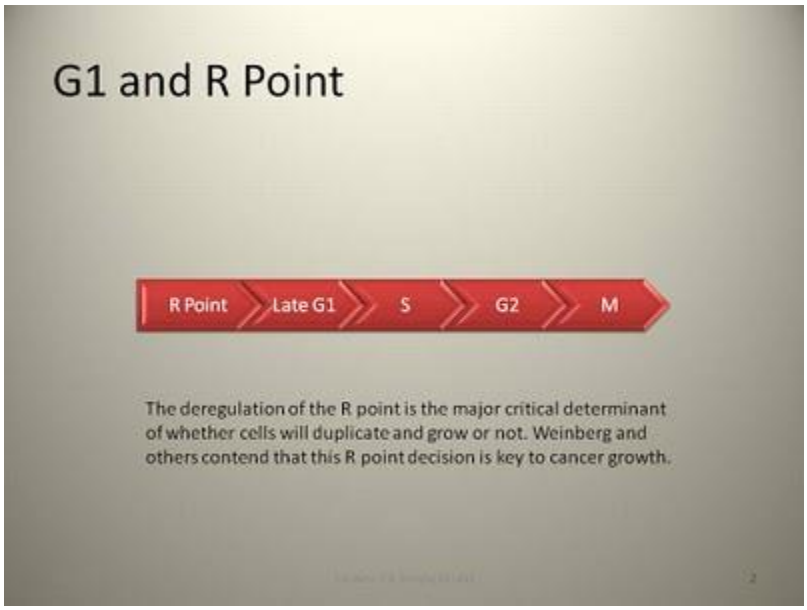
The 2003 NEJM article by Nelson et al on Prostate Cancer lays out the genetic progression of Prostate Cancer and it is that progression which PSA somewhat follows. Yet it is that progression that most histological exams, using say a Gleason framework, do not follow. It is worth a simple review to see what we mean. Let us go through 4 simple steps:

1. Cancer is simply a breaking down of the normal cell cycle as shown below. Cells duplicate themselves via mitosis and it is that mitotic process wherein say old cells "die" and new cells are created. In fact the old cell just repairs itself and then duplicates itself. The classic process is as below.

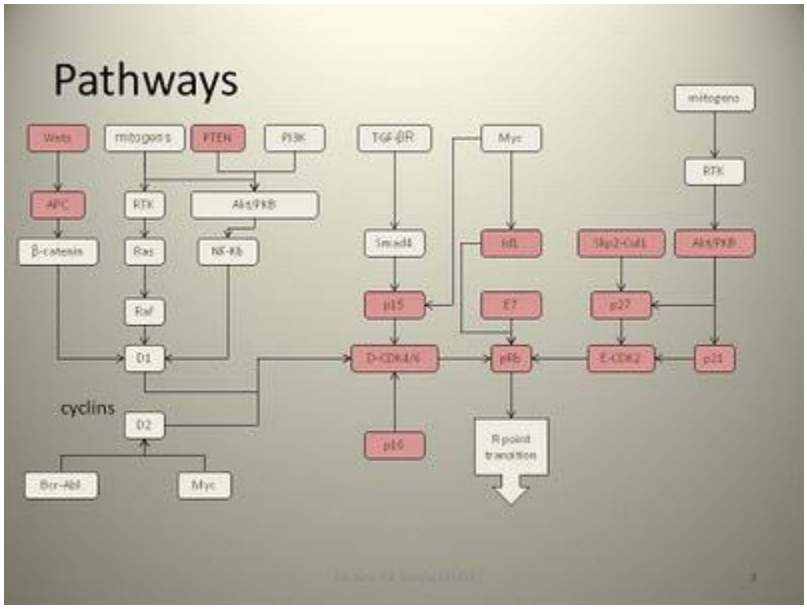


Most of the time the cell is resting in G0. The cell when in G1 is getting ready to reproduce. For it is in S that the DNA copies itself and then goes on to M for separation into new cells. The skin, blood, and many other cells are doing this all the time. However there may be problems. The cell DNA may be hit by radiation, some chemical which damages the DNA, or the like. Cell DNA is quite fragile.

2. The cell begins its change to reproduce and there are many internal control mechanisms. They take the cell almost through G1 up to an R point, at which if the cell DNA has any problems the corrective mechanism will kill the cell. However if the genes controlling this protective mechanism are not working due to same attack, then the cell goes past this R point and does it again and again. That is the beginning of cancer.

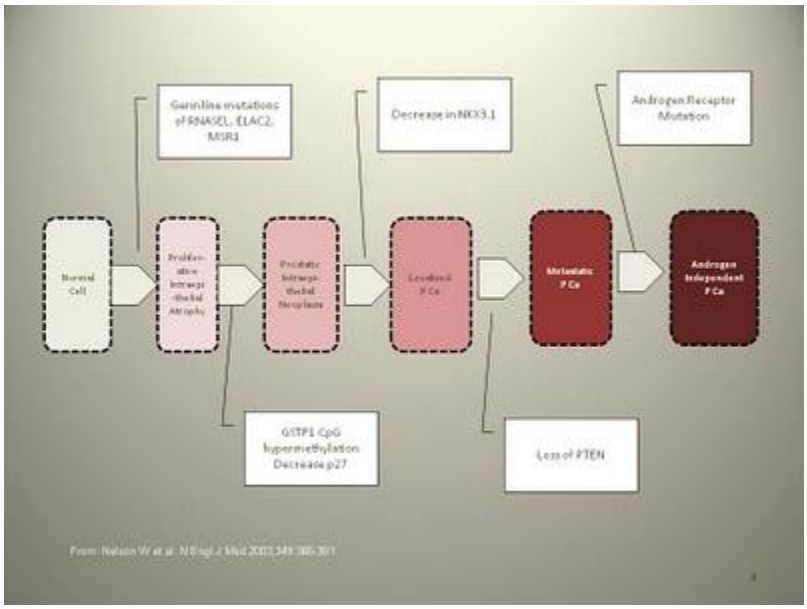


3. Now there are many chemical pathways that try to stop errors from propagating. We show some of them below.



The most important for Prostate Cancer is the PTEN pathway. This gene and its protein if in any way damaged result in loss of control of cell growth. Many environmental factors control the breakdown of PTEN. Once it goes the PSA starts to explode. The cancer then also becomes unmanageable. It is this final assault that will often result in death.

4. Cancer is a progressive disease of steps. The ones from Nelson, and there are updated version of it now seven years later, but this is quite reasonable are shown as follows:



A simple health cell starts on the left and spends its whole life happy and well. Then all we need is one cell which gets attacked and the process starts. But it takes many attacks, one after the other to take the cell from a slight problem to a deadly mass. Understanding these steps and being able to determine what is in the "bad" cells will be a much better path to take than what we have now with PSA but PSA is good. It works, and it does save lives.

Thus we argue three facts:

1. The clan of Comparative Clinical Effectiveness users is really a backward looking clan. In fact the PSA testing controversy shows how backward looking they can be. Yes a 4.0 PSA will result in little improvement. For by the time it gets there especially in young men it is too late. We need a forward looking clan of researchers on the clinical side. That however may be an oxymoron since the clinical researchers most often look backward.

2. The genetic markers are truly the best measures of what the problem may be. Yet we need better means and methods to measure them We need to have say nanotechnology which will scrub through the prostate and scape up telltales of the presence of the genetic markers. Are there any PTEN negative cells, and if so then they are the clones which will be reproducing and kill the patient. They are the ones which should be eliminated.

3. Genetic medicine is as we have argued recently the PC of medicine. It will be the sea change necessary to finally attain scale in the practice of medicine.

4 PROSTATE BIOPSY SAMPLING

The question of detecting prostate cancer upon biopsy is an interesting exercise in sampling. We proceed to develop a simple model to determine the probability of missing cancer upon a biopsy. To accomplish this we have to make a set of basic assumptions. These may be modified and they in turn will modify the results.

We first look at a simple model of cancer and focus on the prostate. The issue is simply at what point should we be concerned. How large a collection of cells is a collection to be concerned about. Thus we first review some issues of growth and size and then we examine the issue of sampling and detection probability.

4.1 Some Preliminary Facts

Cancer is a complicated disease and even at that it is an understatement. The control mechanisms which set cancer in motion flow through the many pathways which are known. Yet there is at the gross level some simplicity which we want to develop here for a clinical purpose of evaluating the effectiveness of prostate biopsies. There are a few basic facts.

1. Cancer is generally clonal, one cell goes wild and keeps reproducing. This is uncontrolled mitosis or cell replication. Thus mitosis and its control is of major concern. The clonal theory states that it is but one cell that goes into an uncontrolled state and that all progeny are progeny from that parent cell. There is some work recently with melanoma which counters this theory but for our present interests we shall keep the clonal approach.

2. The reproduction rate is not quite doubling, some progeny do not survive, thus depending on the status of the tumor the growth rate is between 1 and 2 per generation. Sometimes it is less than 1 and it even regresses as seen in melanoma. The ability of clonal progeny to survive is also a window to cancer control.

3. There are cell cluster sizes which are of interest. As Weinberg notes, when there are 10E6 cells the tumor can be seen under CAT or MRI. When there are 10E9 cells it is palpable, when there are 10E12 the patient dies. Almost always these metrics can be used. Thus when we look at prostate cancer we are looking for the needle in the haystack, hopefully, namely the 1 million cell clusters.

4. Cancer growth and evolution is a classic epigenetic systems process in cell growth and

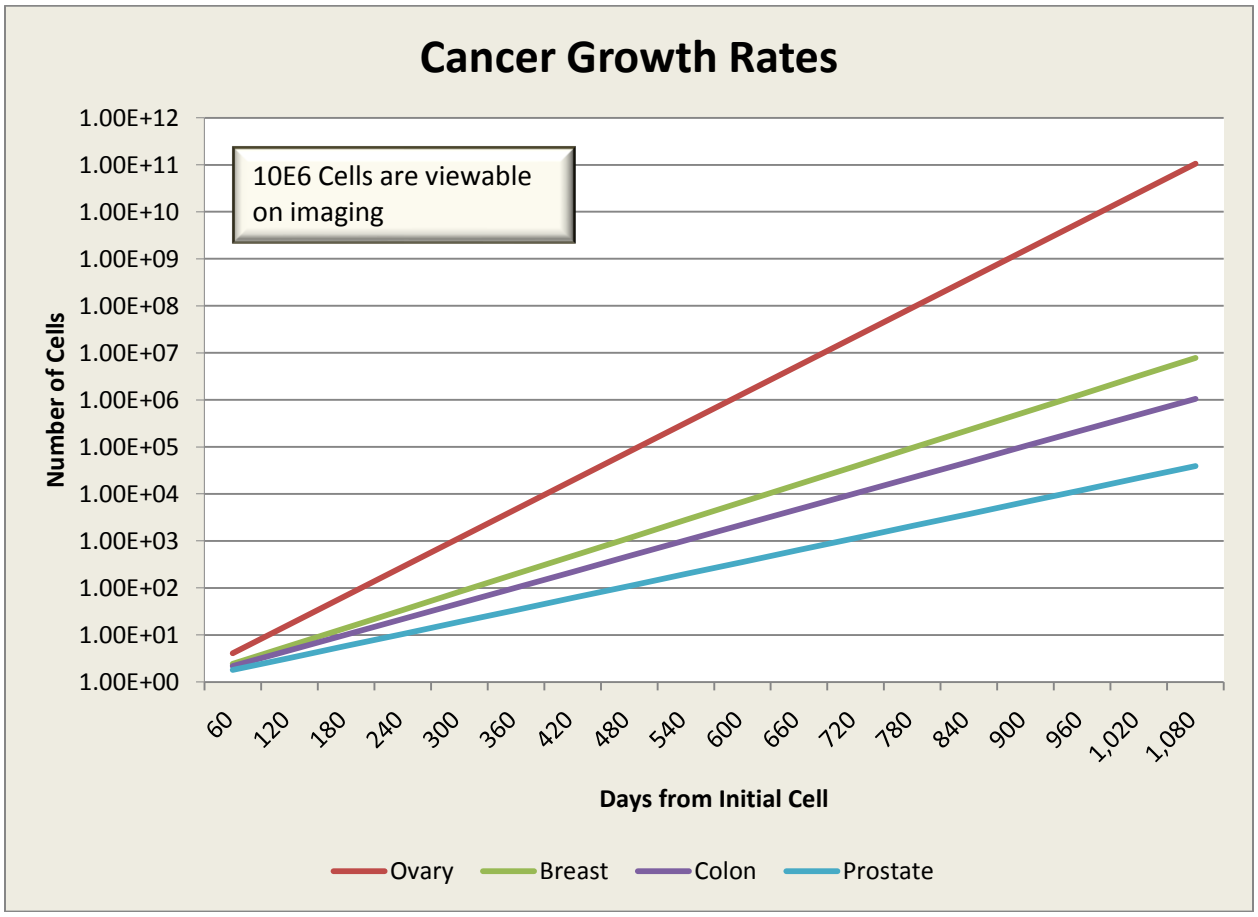
replication. The cell loses its ability to die, it just keeps growing and replicating itself with its functionality reduced to it replication and nothing else.

5. The mitotic cycle, the time from quasi doubling to quasi doubling is different for many cancers. Ovarian cancer has a short doubling time, days. The mitotic cycle itself is about 16 hours and then the initiation of another cycle may start within a few days. This is why ovarian cancer is so aggressive. In contrast indolent prostate cancer may take months between doubling and the reproduction rate itself may be quite low, well less than 2 and slightly more than 1. However, there is an aggressive form or prostate cancer, the details of which are still not well known, where the rate and the reproduction rate make for rapid growth. The rate may be quite short, days or weeks for doubling and the reproduction rate may be near 2.

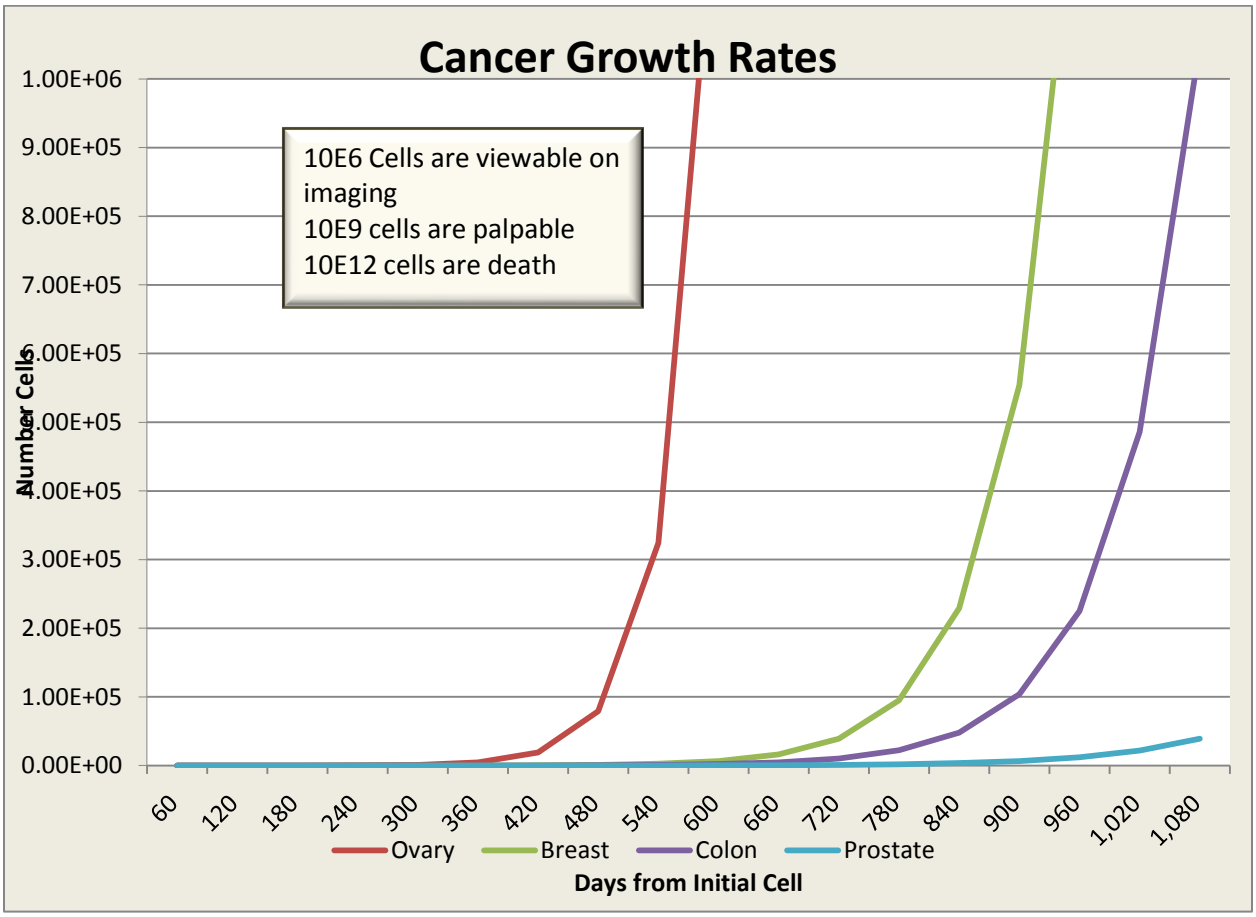
This is the simple story of cancer so that we can look at the 1 million cell cluster. We show a simple growth model for 4 cancers below. We depict the number of cells from the clonal beginning for each of these cancers as a function of time. One can see how ovarian and breast cancers kill so quickly.

Time (Days)	*Ovary*	*Breast*	*Colon*	*Prostate*
60	4.10E+00	2.41E+00	2.16E+00	1.80E+00
120	1.68E+01	5.83E+00	4.67E+00	3.24E+00
180	6.87E+01	1.41E+01	1.01E+01	5.83E+00
240	2.81E+02	3.40E+01	2.18E+01	1.05E+01
300	1.15E+03	8.21E+01	4.70E+01	1.89E+01
360	4.72E+03	1.98E+02	1.02E+02	3.40E+01
420	1.93E+04	4.79E+02	2.20E+02	6.12E+01
480	7.92E+04	1.16E+03	4.74E+02	1.10E+02
540	3.25E+05	2.79E+03	1.02E+03	1.98E+02
600	1.33E+06	6.75E+03	2.21E+03	3.57E+02
660	5.44E+06	1.63E+04	4.78E+03	6.43E+02
720	2.23E+07	3.93E+04	1.03E+04	1.16E+03
780	9.13E+07	9.50E+04	2.23E+04	2.08E+03
840	3.74E+08	2.29E+05	4.82E+04	3.75E+03
900	1.53E+09	5.54E+05	1.04E+05	6.75E+03
960	6.28E+09	1.34E+06	2.25E+05	1.21E+04
1,020	2.57E+10	3.23E+06	4.86E+05	2.19E+04
1,080	1.05E+11	7.80E+06	1.05E+06	3.93E+04
1,140	4.31E+11	1.88E+07	2.27E+06	7.08E+04
1,200	1.77E+12	4.55E+07	4.90E+06	1.27E+05
1,260	7.24E+12	1.10E+08	1.06E+07	2.29E+05
1,320	2.96E+13	2.65E+08	2.29E+07	4.13E+05
1,380	1.21E+14	6.41E+08	4.94E+07	7.43E+05
1,440	4.97E+14	1.55E+09	1.07E+08	1.34E+06
1,500	2.04E+15	3.74E+09	2.30E+08	2.41E+06
1,560	8.34E+15	9.03E+09	4.98E+08	4.34E+06
1,620	3.42E+16	2.18E+10	1.08E+09	7.80E+06
1,680	1.40E+17	5.27E+10	2.32E+09	1.40E+07
1,740	5.73E+17	1.27E+11	5.02E+09	2.53E+07
1,800	2.35E+18	3.07E+11	1.08E+10	4.55E+07
1,860	9.62E+18	7.42E+11	2.34E+10	8.19E+07
1,920	3.94E+19	1.79E+12	5.06E+10	1.47E+08
1,980	1.61E+20	4.33E+12	1.09E+11	2.65E+08
2,040	6.61E+20	1.04E+13	2.36E+11	4.78E+08
2,100	2.71E+21	2.52E+13	5.10E+11	8.60E+08
2,160	1.11E+22	6.09E+13	1.10E+12	1.55E+09
2,220	4.54E+22	1.47E+14	2.38E+12	2.79E+09

Note that in this model we assume rapid growth for ovarian cancer and slow growth for prostate. This may not always be the case. For example there are certain prostate cancers which grow very aggressively, the reasons are not yet known. We show the growth below in two scales.



The above is on logarithmic scale and the one below is linear.



This shows two factors. One is that certain cancers grow so quickly that one must have to screen on a quarterly basis to have any effect. That is very costly. Second some cancers grow so slowly that screening will result in surgeries that are not necessary since the cancer will never grow large enough to kill the person. Thus between too fast and too slow are many others, and too fast may not be too fast and too slow may not be too slow. That is the conundrum.

In a recent JAMA article the authors state[12]:

"*Early detection may not be the solution for aggressive cancers because many may not be detected early enough for cure. Some small "curable" breast cancers, categorized as low risk by National Institutes of Health criteria, have a high mortality risk when analyzed using prognostic molecular profiles such as the NKI 70 gene test. Biologically aggressive cancers present with a higher stage despite screening. Interval cancers, those that present clinically between routine screens, have a higher growth fraction and are more likely to be lethal compared with screen detected cancers. In the neoadjuvant I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and*

[12] http://jama.ama-assn.org/cgi/content/full/302/15/1685

Molecular Analysis) trial, in which the mean tumor size was 6 cm (accrual 2003-2006 in the United States), 91% had poor prognosis biology[27] (using the NKI 70 gene test), which is much higher than the 33% poor prognosis proportion in women undergoing routine screening.[21] Of women undergoing routine screening in the I-SPY TRIAL, 85% of the malignancies were interval cancers and only 15% were screen detected, suggesting that locally advanced cancers reflect the growth curve.... Similarly, the most lethal prostate cancers are those with rapidly increasing...

Screening is most successful when premalignant lesions can be detected and eliminated as in the case of adenomatous polyp removal during colonoscopy screening or cervical intraepithelial neoplasia ablation by colposcopy after detection by pap smear. Perhaps most important is that screening for cervical and colon cancer and the removal of pre-neoplastic lesions have been accompanied by a significant decrease in their invasive cancer counterparts; this has not been seen in breast and prostate cancer. Ductal carcinoma in situ, rare prior to widespread screening, now represents 25% to 30% of all breast cancer diagnoses (>60 000 new case-diagnoses annually are not included in the invasive cancer statistics), the majority of these lesions are low and intermediate grade. Ductal carcinoma in situ is considered to be a precancerous lesion and standard of care is excision and adjuvant treatment. However, after 2 decades of detecting and treating DCIS, there is no convincing evidence of substantial reduction in invasive breast cancer incidence. The 2002 decrease in incidence leveled off in 2005 and is attributed to a reduction in postmenopausal hormone therapy use, not DCIS removal."

The authors then suggest actions which we have detailed earlier in McGarty, Health Care, they rephrase them as follows:

Biomarkers to Differentiate Significant- and Minimal-Risk Cancers. To help move toward a more effective solution, the first step is a change in mindset in scientific discovery efforts and clinical practice

Reduce Treatment Burden for Minimal-Risk Disease. Many diagnosed tumors will follow an indolent course for the patient's lifetime[42] or are probably cured with surgical excision alone.

Develop Tools to Support Informed Decisions. Information about risks of screening and biopsy should be shared with patients before screening. At the time of cancer detection, risks and benefits of treatment for specific biological subtypes should be shared

Focus on Prevention for the Highest-Risk Patients. Ultimately, prevention is preferable to screening by reducing the risk that a patient will have a diagnosis, experience undesirable effects of treatment, and confront the specter of recurrence. For both breast and prostate cancer, available agents are proven to reduce cancer risk: finasteride and tamoxifen or raloxifene.

Demonstration Projects: Tactics for the New Strategy. To reduce morbidity and mortality from breast cancer and prostate cancer and to execute the proposed strategy, a comprehensive approach, using large demonstration projects to create a learning system, integrating both clinical care and research is needed. By spanning the spectrum from screening to treatment and survivorship, learning from diagnosis, treatment, and outcomes can be applied to developing tailored strategies for screening and prevention."

The problem is a bit more complex, however. It requires screening first, then staging. Screening is a difficult one since what is known today about the genetics of cancer growth for the most part reflects what is activated in a rapidly growing cancer. There are certain genetic predisposing genes but the problem is what turns them on and when.

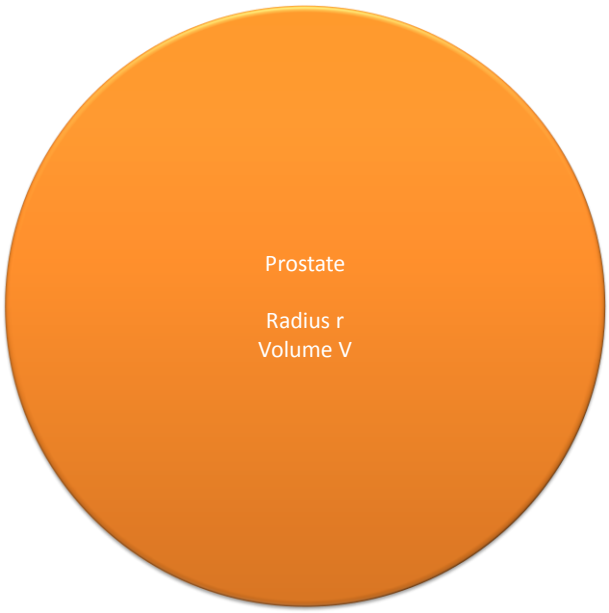
4.2 Basic Assumptions

We now make certain assumptions.

1. Assume a spherical prostate. This is not unrealistic and we then state that the prostate volume is V and it has an effective radius of r. Recall that:

$$V = \frac{4}{3}\pi r^3$$

We depict such a model below.



2. Now assume that there are cells in the prostate and that a cell is of a radius rcell and that the number of cells in the prostate is determined as:

$$N_{cells} = \frac{V_{prostate}}{V_{cell}} = \frac{r^3_{prostate}}{r^3_{cell}}$$

We present some of the basic assumptions below. We assume a standard prostate of 40 cc and a standard cell size of 100 µm and from this we can readily obtain number of cells of almost 10 million in a prostate. There may be fewer due to packing ratios and glands but for the purpose of the analysis this is not unreasonable.

3. When performing a biopsy we use a needle of 1.2 mm in diameter and of length 15 mm for each core sample[13].

	Basic Units	Units um	
Prostate Size (cc)	40.00	40,000,000,000,000	
Prostate Radius	2.12	21,219	
Cell Size um	100.00		
Cell Volume		4,186,667	
Cells per Prostate		9,554,140	
Probe Diameter mm	1.20	12	
Probe Length mm	15.00	15.00	
Core volume cmm		1,696	
Core Volume cum		1,695,600,000,000	
Core Vol % Prostate Volume			4.239%
Cells in Core		405,000	
Number Cores	14.00		
Total Cells in All Cores		5,670,000	
Percent Cells Sampled			59.346%
Tumor Size in Cells		1,000,000	
Tumors Size as % Prostate			10.47%

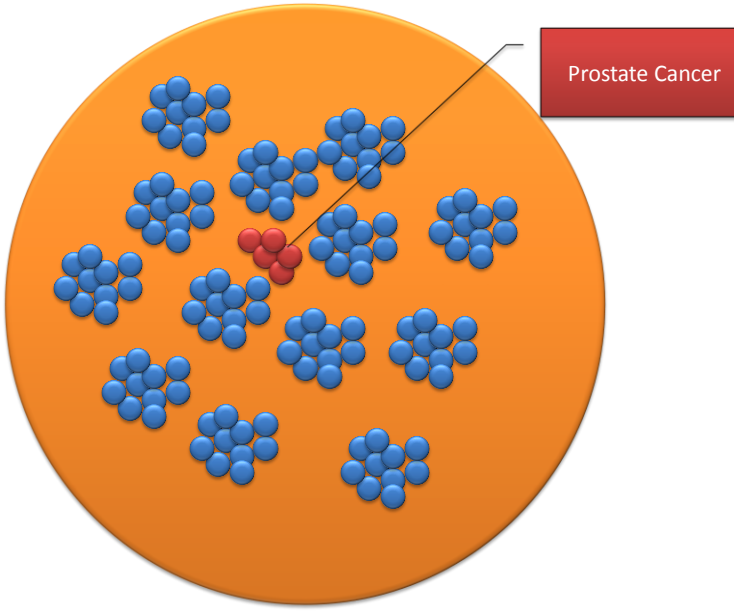
4. Assume that the tumor cells are of the same size as normal cells and that the tumor volume has reached a minimal perceptible size of 1 million cells.

We now set the level of cells as 1 million or 10% of the prostate cell size for a 40 cc prostate. We can alter this based upon a set level. This means that 10% of a normal

[13] http://www.jurology.com/article/S0022-5347%2807%2900738-0/abstract

prostate is composed of cancer cells. Based upon our analysis done above, this may or may not be an important issue. It is the result of 20 binary cell divisions. There may have been thirty cell divisions to get to that mass. The time between divisions may be weeks or months depending on the loss of control in the cell. If we assume a month between division then we have a three year window from when the first malignant cell was created and when a sample of 1 million are present.

We graphically depict this situation below. We show a cluster of normal cells and a single malignant cluster. It should be noted that there may be diffuse malignant clusters and not just one depending on the growth.



4.3 Analysis of the Detection

We now proceed to determine the detection of the malignant cells as well as the probability of not detecting them.

The literature states:

The rectal wall is thin, so it is possible to place the needle more accurately and with less injury to other tissues. When activated, the needle can remove a slender cylinder of tissue (about 1/2" by 1/16"), called a core, in a fraction of a second. Biopsy needles are

tiny -- only 1.2 millimeters in diameter and less than 1/2" long -- and very precise. A sliding sheath opens once the needle enters the prostate, closes onto a sample of tissue and the needle is withdrawn[14].

And

It is widely reported that a prostate biopsy gun needle advances 0.5 cm and then obtains the subsequent 1.5 cm of tissue. Based on this presumed skip area it is recommended that the needle tip must be placed 0.5 cm from the capsule before firing to obtain the capsule with the specimen. Contrary to this longstanding recommendation, in our experience we have observed that there is no such skip area. We determined the actual content of a needle core by obtaining biopsies from an apple model with clinical correlation to validate our findings[15].

We make the following assumptions.

1. Assume that we use a core which has a diameter of some know amount and a core length of some known amount. This yields the volume per core.

2. Assume that the prostate has a known volume and that the cell has a known radius. Assume that the cells have a volume based upon their spherical radius and that the number of cells is simply the ratio of the prostate spherical volume to the volume of a single cell. We know that the number of cells may be a fraction lower due to packing and due to a mixture of cells in the stroma. However we can always adjust for that change.

3. Assume that we use several cores and that the location of the cores are independent and non-overlapping.

4. Assume total randomness in the cancer location. Assume that there are 1 million cancer cells as we have suggested above.

Then we want to find the probability that we can detect the 1 million cancer cells using the above set of assumptions.

[14] http://www.upmccancercenters.com/cancer/prostate/biopsyneedle.html

[15] http://www.jurology.com/article/S0022-5347%2807%2900738-0/abstract

Let

$$V_{Cell} = \frac{4}{3}\pi r^3_{Cell}$$

$$V_{Prostate}\frac{4}{3}\pi r^3_{Prostate}$$

$$N_{Cells} = \frac{V_{Prostate}}{V_{Cell}}$$

$$Cell\ density = \rho_{Cell} = \frac{N_{Cell}}{V_{Prostate}}(cells/cc)$$

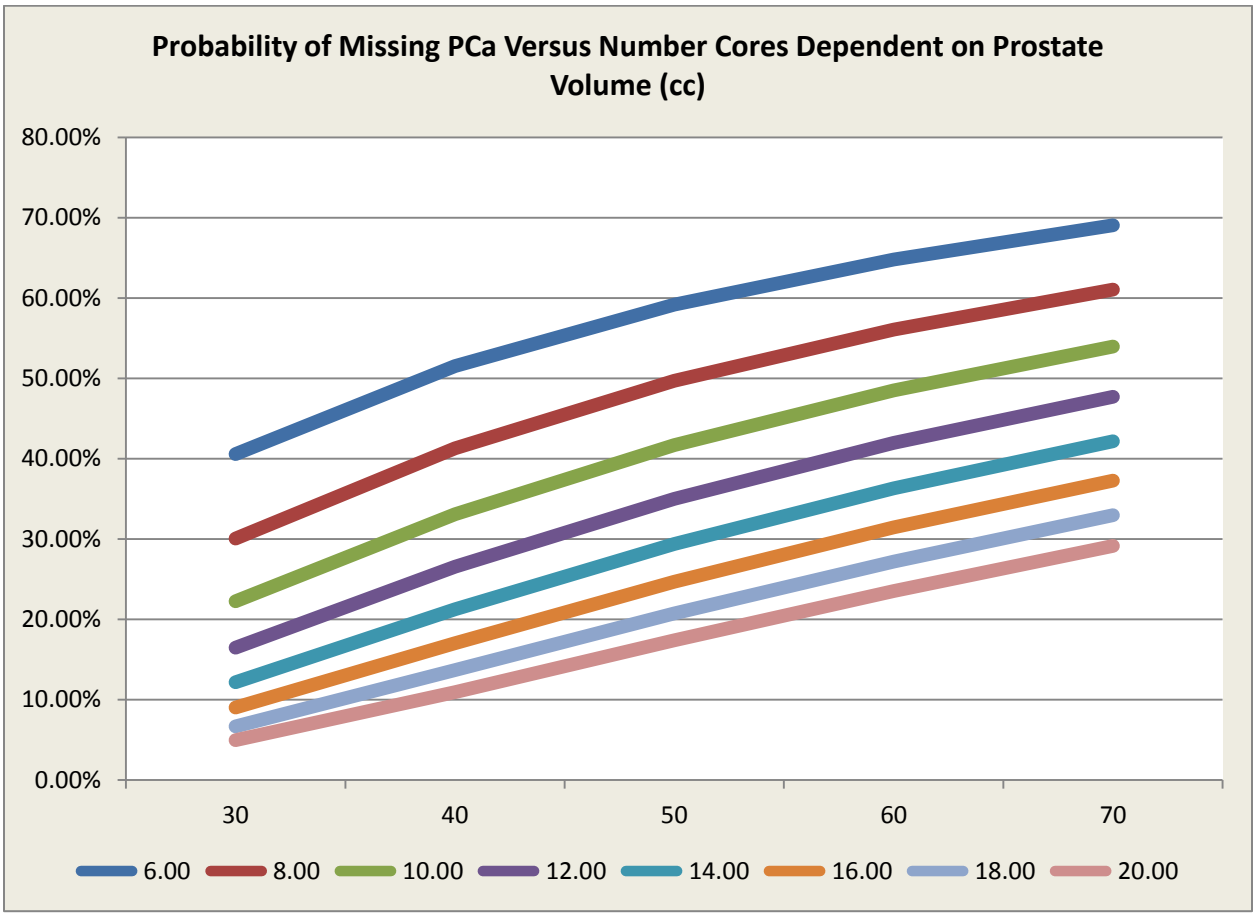
Now we assume that the cluster of cancer cells is uniformly distributed across the prostate so that the probability of placing a core in a cancer cell is determined by the chance of hitting the cancer cells with a probe. We determine this as follows:

$$p = P\left[Hitting\ a\ Cancer\ Cluster\ with\ one\ core\right] = \frac{N_{CancerCells}}{N_{ProstateCells}}$$

$$P\left[Miss\ a\ cluster\ with\ single\ core\right] = 1 - p$$

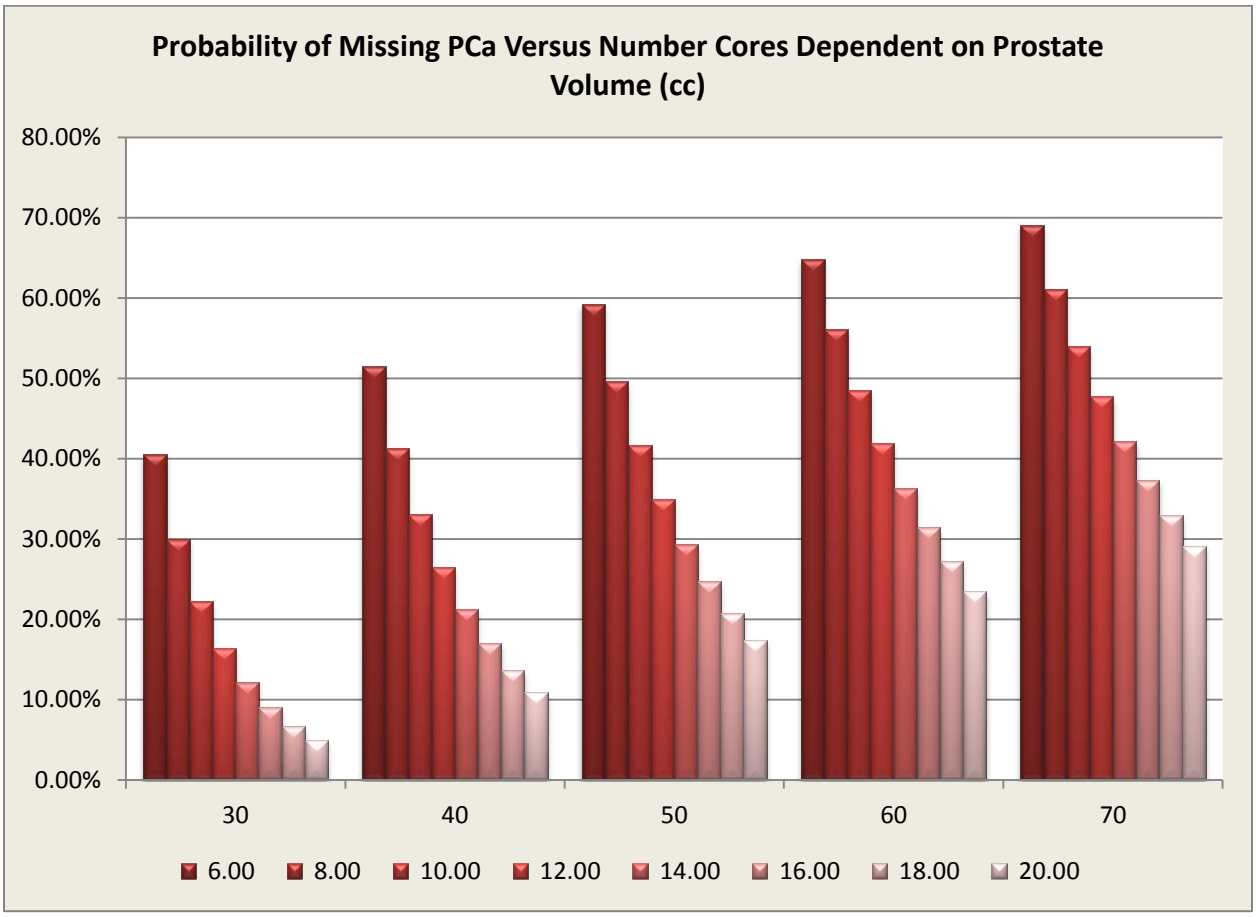
$$P\left[Miss\ Cluster\ with\ N\ Cores\right] = \left(1-p\right)^N$$

Then using the data provided above for the samples we obtain the following curves for the miss probability.



The high miss rate even for average prostates for 10-12 cores is significant. This will play a role in later studies which often neglect this dominant factor. The only gold standard is the biopsy of the total prostate. This is why when a prostatectomy is performed the Gleason grade is often increased. The samples are just too small.

We also show below the same data as above but we present it in a different manner. Here we show by different prostate volumes the required number of cores to reach a certain level of cancer miss.

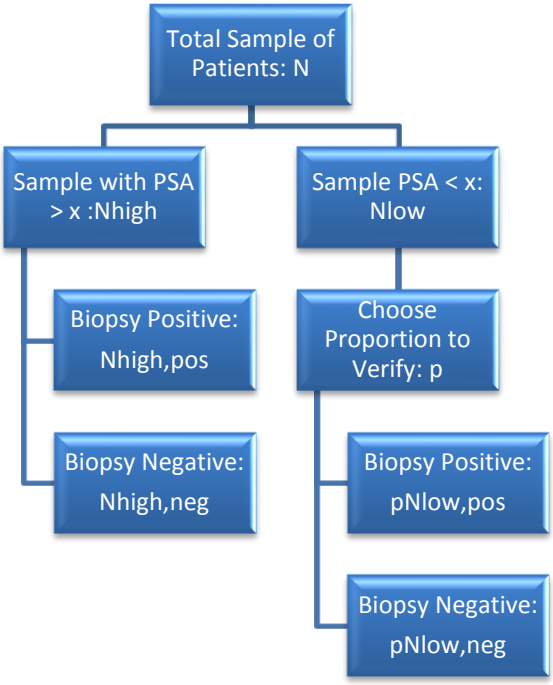


Thus we will argue that the prostate biopsy, albeit useful, it not a gold standard. It has not generally biopsied the tumor space even if assisted with ultrasound.

5 VERIFICATION BIAS

There are many biases in statistical tests and the verification bias is but one, but a critical one in medical testing. Let us consider a test whose usefulness we wish to test in determining the presence of a disease. In this case we will assume that we use a PSA test and we are looking for prostate cancer. We may use the test to screen and if the PSA is above a certain level we will them do a biopsy. We would assume the biopsy is the gold standard but as we have just shown it is clearly not due to its own sampling errors. With those whose test is below a threshold we should do a biopsy but that is costly and invasive so we choose a small sample only. This may most likely lead to a test with a verification bias.

The procedure may look as follows:



5.1 The Problem

The problem is that although we choose all high values to test and validate we choose only a portion of the low values to test.

We seek a Table of the following form:

		Disease State	
		Present	Absent
Test Result	Positive	N(P,P)	N(A,P)
	Negative	N(P,N)	N(A,N)

Now the above assumes we use all patients in a large sample. What if we use all who are positive but the fraction who are negative. We get the following table:

Test Result	Disease State		
		Present	Absent
	Positive	N(P,P)	N(A,P)
	Negative	Np(P,N)	Np(A,N)

Where Np represents the proportion of the negative test sampled. It should be noted that if we choose p as the fraction sampled that we are not in any way assured that Np=p*N. That is the fraction who are diseased in the subset may not equal the pro-rated fraction diseased from the larger set.

Now we wish to determine the following:

$$Number\left[D = PCa \middle| PSA > n\right] = n_{PCa+,PSA+}$$
$$Number\left[D = PCa \middle| PSA < n\right] = n_{PCa+,PSA-}$$
$$Number\left[D = noPCa \middle| PSA > n\right] = n_{PCa-,PSA+}$$
$$Number\left[D = noPCa \middle| PSA < n\right] = n_{PCa-,PSA-}$$

and

$$Sensitivity = \frac{n_{PCa+,PSA+}}{n_{PCa+,PSA+} + n_{PCa+,PSA-}}$$

and

$$Specificity = \frac{n_{PCa-,PSA-}}{n_{PCa-,PSA-} + n_{PCa-,PSA+}}$$

However this is a measure based upon samples and not a measure based upon probabilities. Let us consider a simple example of trying to detect two signals in noise. Let is assume we have:

$$s_0(t) + w(t)$$
$$and$$
$$s_1(t) + w(t)$$
$$and$$
$$r = \int_0^T r(t)dt$$
$$and$$
$$r_1 = s_1 + w$$
$$and$$
$$r_0 = s_0 + w$$

We will assume that when we do this we have the following for the variables, and we assume w is Gaussian with mean 0 and standard deviation σ. We then define the detection probability and the false alarm probability as follows:

$$P[D] = P[s_1|s_1] = P[Say\ s_1|Was\ s_1]$$
$$P[FA] = P[s_1|s_0]$$

These are the detection and false alarm probabilities. The detection probability is also the sensitivity. Now:

$$Assume\ s_0 = 0$$
$$Assume\ s_1 = E$$
$$Then:$$
$$p(r/s_1) = \frac{1}{\sqrt{2\pi\sigma}}\exp(-\frac{1}{2\sigma}(r-E)^2)$$
$$and$$
$$p(r/s_0) = \frac{1}{\sqrt{2\pi\sigma}}\exp(-\frac{1}{2\sigma}(r)^2)$$

Then we can plot P[D] versus P[FA] and this is the ROC or receiver operating characteristic. We do this calculation by varying the selection boundary of choosing what was sent. Analytically we have:

$$P[D] = \int_T^\infty p(r / s_1)dr$$
$$P[FA] = \int_T^\infty p(r / s_0)dr$$

Clearly if we make T small then we get a better P[D] but we get a larger P[FA] as well. It of course also depends on E and the variance of the noise.

Now returning to the counting case, we can determine the probabilities from the data. Simply:

$$P[D] = \int_T^\infty p(r / s_1)dr$$

as

$$\hat{P}[D] = \frac{Number\ of\ Cases\ PCa\ when\ PSA>x}{Total\ Number\ of\ PCa\ for\ all}$$

but

$$P[D] = \lim_{n\to\infty} \hat{P}[D;n]$$

That is the measure variable approaches the true statistic only as the sample gets very large. Thus even if we were to sample all in all categories we would have some error due to limited sampling.

We now have a different problem. Let us return to the analysis we presented at the commencement of the section. Here we have a set of N patients upon whom we perform a diagnostic test, the PSA, and then we break it into two groups, those above and below a threshold, and then we biopsy all those above and only a select number below. What can we say about this test. The term validation bias has been used to determine if we have created some distortion on the end result. Frankly we totally disregard a set of the tested but un-biopsied group then clearly we have created a bias. If so how do we modify that?

Recall:

$$\hat{P}[D] = \frac{Number\ PSA>x\ and\ Biopsy\ Positive}{Number\ PSA>x\ and\ Biopsy\ Positive + Number\ PSA<x\ and\ Biopsy\ Positive}$$

But we have delimited part of the above denominator by selecting out a limited number as follows:

$$\hat{P}[D] = \frac{Number\ PSA>x\ and\ Biopsy\ Positive}{Number\ PSA>x\ and\ Biopsy\ Positive + Number\ PSA<x\ and\ Biopsy\ Positive\ and\ in\ Group\ V^{+}}$$

Clearly we will then overestimate P[D] because there may be fewer in the group. There is also the problem that we may not have detected cancers because as we have shown before, a negative biopsy does not mean cancer. We should be saying a negative biopsy and not PCa! We will return to that later.

5.2 Approaches to Eliminating Verification Bias

There are several ways to address the bias. We examine two of them here. The first is that of Punglia. In that paper they take data and then adjust the cells that have not been verified in a manner using the other variable they have at hand. The second approach uses a maximum likelihood approach by Jhou.

5.2.1 Punglia Approach

The Punglia model is shown below. We have presented it as they have. Note the large number not tested.

		Disease	
		Present	Absent
Test	Positive	92	27
	Negative	46	72
	Not Tested	89	108

Now recall:

$$Sensitivity = \frac{Number(TestPositive; Disease\ Present)}{Number(Disease\ Present)}$$

$$Specificity = \frac{Number(DiseaseAbsent; TestNegative)}{Number(DiseaseAbsent)}$$

For this case:

Sensitivity=92/(92+46)=67%
Specificity=72/(72+27)=71%

Now they adjust the negatives, which are all the not tested as follows. They take the patients not sampled, all of whom have a negative test, and then adjust the entries to reflect the occurrence of PCa in such a group.

We can detail the Punglia data as follows, which makes it align with the Jhou formulation.

		Test		
		Positive	Negative	Total
Disease	Present	92	46	138
	Absent	27	72	99
	Not Tested	0	197	197
	Total	119	315	434

Note that we here align the 197 total negative tests in the not tested category. There were 434 total patients. Now the question is how to assign the 197 non tested to PCa and to non PCa status. The authors make the jump apparently by using a logistic analysis based upon several variables; namely DRE, race, family history, and category of PSA, as well as aged (under and over 60). Thus they created a logistic model where:

$$ln\frac{P[PCa]}{1-P[PCa]} = \alpha + \sum_{i=1}^{N} \beta_i x_i$$

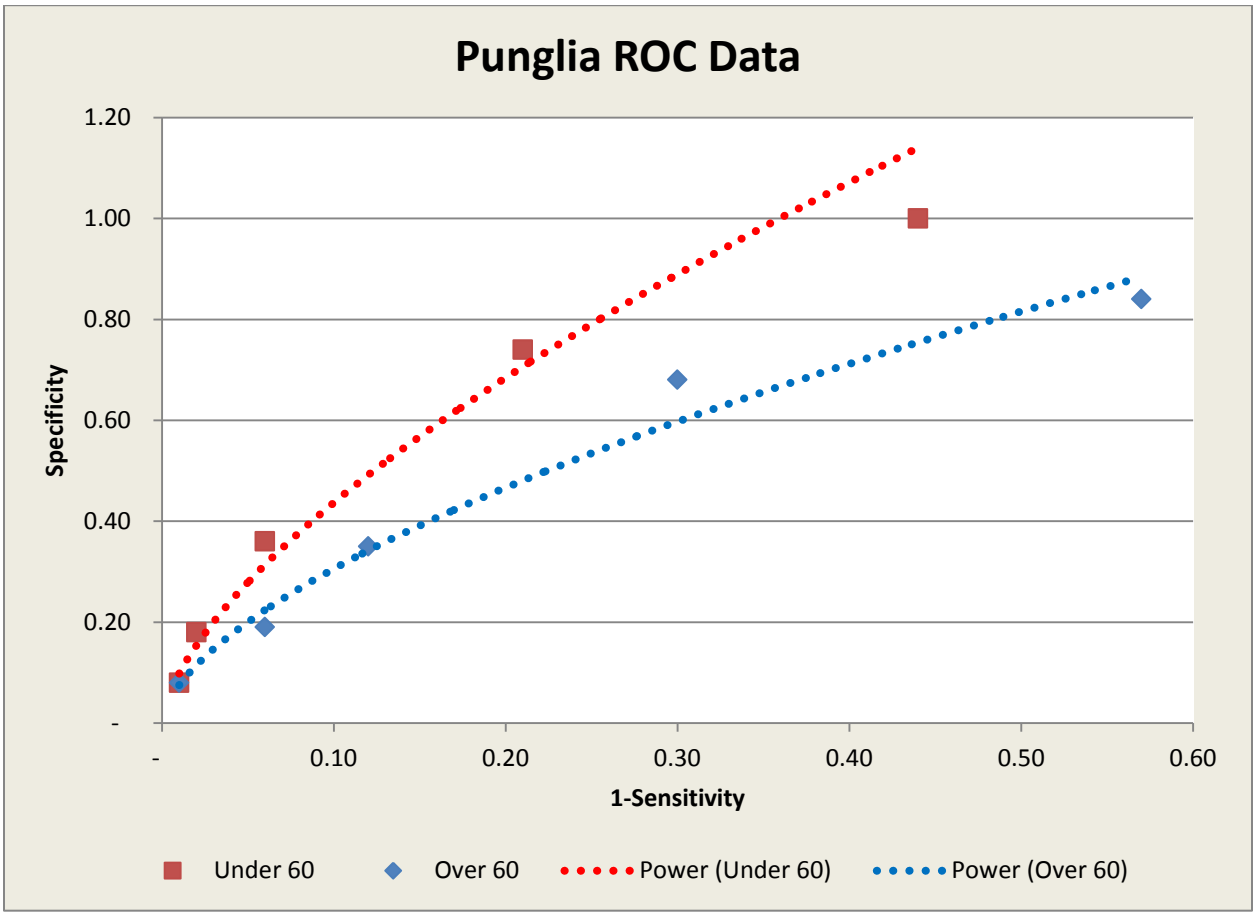
They then did a regression analysis on some data set to determine the logistic constants and adjusted the table accordingly. The result is below:

		Test		
		Positive	Negative	Total
Disease	Present	92	115	207
	Absent	27	180	207
	Total	119	295	414

This yields a Specificity of 87% and a Sensitivity of 44%. The problem is that placing so many with negative biopsies in the Disease state is done under the logistic analysis and is questionable.

Under 60			Over 60		
PSA	Sensitivity	Specificity	PSA	Sensitivity	Specificity
0.90	100%	56%	1.10	84%	43%
1.40	74%	79%	2.10	68%	70%
2.60	36%	94%	4.10	35%	88%
4.10	18%	98%	6.10	19%	94%
6.10	8%	99%	10.10	8%	99%

What Punglia states ion the above is that there is great variability in the levels of PSA and the ability to test for PCa. Namely, if the patient is under 60, then the level should be lowered substantially for follow up with biopsy. Yet recall, as we have shown, the biopsy has itself a 25% failure rate to detect PCa.



5.2.2 Zhou Approach

The Zhou approach uses a maximum likelihood detector. Whereas the Punglia approach uses a variant of the Greenes and Begg approach, the Zhou approach is fairly direct in using a ML analysis.

		Test=Positive (1)	Test=Negative (0)
V=1	Diagnosis=Positive(1)	X11	X10
V=1	Diagnosis=Negative(0)	X01	X00
V=0 (Not in Validation)		XB1	Xb0
Total		n1	n0

Note we have in the not validated section some which have positive tests and some with negative. The question is how to assign them across the groups but to do so such that Sensitivity and Specificity are estimated. Also not that if the XB are both zero then the best we could do is to calculate the two desired variables directly from the data.

To understand Zhou we follow his simplified analysis:

Let V be the group selected and let D be the diagnosis and T the test.

Then

$$P\left[V=1\middle|D,T\right]=P\left[V=1\middle|T\right]$$

or that the selection to V is independent of diagnosis D

We want the following:

$$Se=P\left[T=1\middle|D=1\right]$$

$$Sp=P\left[T=0\middle|D=0\right]$$

The above defined specificity and sensitivity in classic probabilistic terms. We follow Zhou's notes accordingly:

Note :

$$Se=\frac{No(T=1,D=1)}{No(D=1)}$$

In reality this is the estimate of Se

Now we assume independence of V on D the diagnosis. It may depend solely upon T the test. Thus we can write using classic probability notation the following:

$$\frac{No(V=1,T=1,D=1)}{No(D=1,T=1)}=\frac{No(V=1,T=1)}{No(T=1)}$$

or

$$P(V,T,D)=P(V,T)P(D|V,T)=P(V,T)P(D|T)$$

$$P(D,T)=P(D|T)P(T)$$

thus

$$\frac{P(V,T,D)}{P(D,T)}=\frac{P(V,T)}{P(T)}$$

Thus we can write the following using the Zhou notation we have adopted[16]:

$$No(D=1,T=1)=No(V=1,T=1,D=1)\frac{No(T=1)}{No(V=1,T=1)}=x_{11}\frac{n_1}{x_{11}+x_{01}}$$

In a similar manner we have:

$$No(D=1,T=0)=No(V=1,T=0,D=1)\frac{No(T=0)}{No(V=1,T=0)}=x_{10}\frac{n_0}{x_{10}+x_{00}}$$

We also can determine the following:

$$No(D=1)=x_{11}\frac{n_1}{x_{11}+x_{01}}+x_{10}\frac{n_0}{x_{10}+x_{00}}$$

We can now use these in determining Sp and Se as follows[17]:

[16] Note that we are proportioning the total n in the sample on a pro rata basis. This is allowable since we have made the reasonable assumption of independence on V.

[17] It should be noted that this reduces to the standard calculation if we have no un-validated samples.

$$Se = \frac{\frac{x_{11}n_1}{x_{11}+x_{01}}}{(x_{11}n_1)/(x_{11}+x_{01})+(x_{10}n_0)(x_{10}+x_{00})}$$

$$Sp = \frac{\frac{x_{00}n_0}{x_{10}+x_{00}}}{(x_{01}n_1)/(x_{11}+x_{01})+(x_{00}n_0)(x_{10}+x_{00})}$$

These are the Begg-Greenes estimators. Also called B&G estimators. We now compare the three estimators:

	Direct	Zhou Estimate	Punglia Estimate
Sensitivity	66.7%	84.0%	44.4%
Specificity	72.7%	50.4%	87.0%

Note the substantial difference. The BG estimate follows from the above. The Punglia uses the logistic fill and the Direct disregards the data not validated. The Zhou approach appears to be of more credibility. However there is a substantial spread in all estimates. The only solution is to biopsy all in both groups.

There is also the case of determining the ROC, or the receiver operating characteristics. This is the plot of Sensitivity versus 1-Specificity. To do this one must look at the data and then vary the decision point and plot the result. In a more classic case, we would have chosen a metric for the decision point and then mapped out the ROC as some variation in signal to noise. In this case we have not such variant only the cutoff point, namely the PSA level for determining when to take the next step.

5.3 Bayesian Approach

We now look briefly at a Bayesian approach suggested by Vollmer. This has not received as much attention as the previous write ups but it has substantial merit.

Vollmer starts with the expression:

$$P\left[PCa\middle|PSA>x\right] = \frac{P\left[PSA>x\middle|PCa\right]P\left[PCa\right]}{P\left[PSA>x\middle|PCa\right]P\left[PCa\right]+P\left[PSA>x\middle|NoPCa\right]P\left[NoPCa\right]}$$

This gives the Bayes approach of determining the probability of PCa given a specific value of PSA. This can then be parameterized. The term on the left is called by Vollmer as the Positive Predictive Value, PPV.

Vollmer now reorganizes the equation as follows:

$$P\left[PCa\middle|PSA>x\right]=\frac{1}{1+\frac{FP\ \ (1-P\left[PCa\right]}{Sen\ \ P\left[PCa\right]}}$$

where

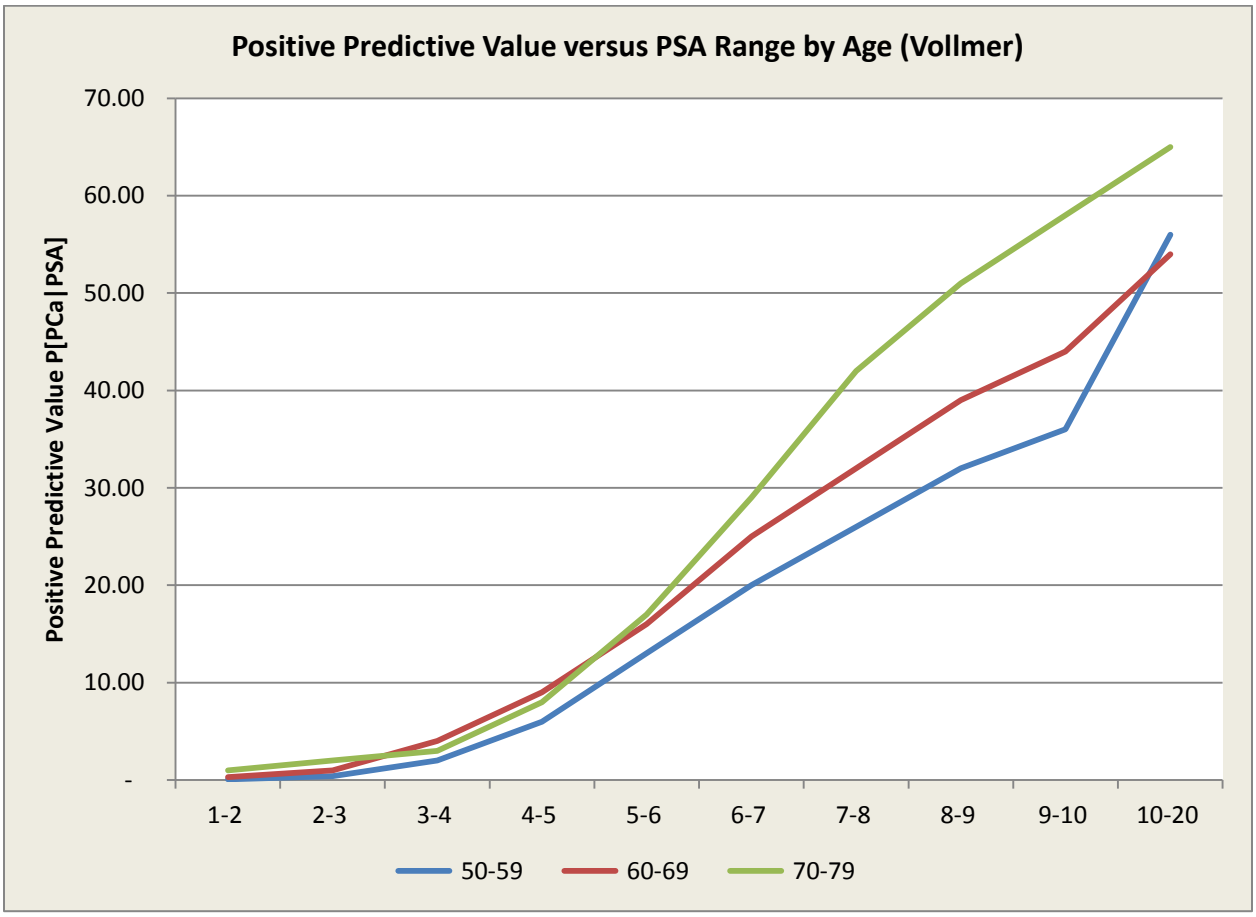
$Sen = Sensitivity = P\left[PSA>x\middle|PCa\right]$

$FP = P\left[PSA>x\middle|No\ \ PCa\right]$

Thus we can obtain the PPV by knowing:

1. The probability of cancer over some defined cohort
2. The sensitivity
3. The FP or false positive probability which also is 1-specificity.

Note that this approach makes some drastic assumptions. Clearly the determination of PCa over some cohort is obtainable via SEER or other types of data bases. The FP is a result of some well-defined and broad based trials. The sensitivity is also derived from many studies.



6 THE AMERICAN AND EUROPEAN STUDIES

The New England Journal of Medicine published two studies today on prostate cancer screening. Before presenting their results for analysis let me first show what the NY Times said. Their headline was: "Prostate Test Found to Save Few Lives"

First the NY Times author, Gina Kolata, states:

"The PSA test, which measures a protein released by prostate cells, does what it is supposed to do — indicates a cancer might be present, leading to biopsies to determine if there is a tumor. But it has been difficult to know whether finding prostate cancer early saves lives. Most of the cancers tend to grow very slowly and are never a threat and, with the faster-growing ones, even early diagnosis might be too late."

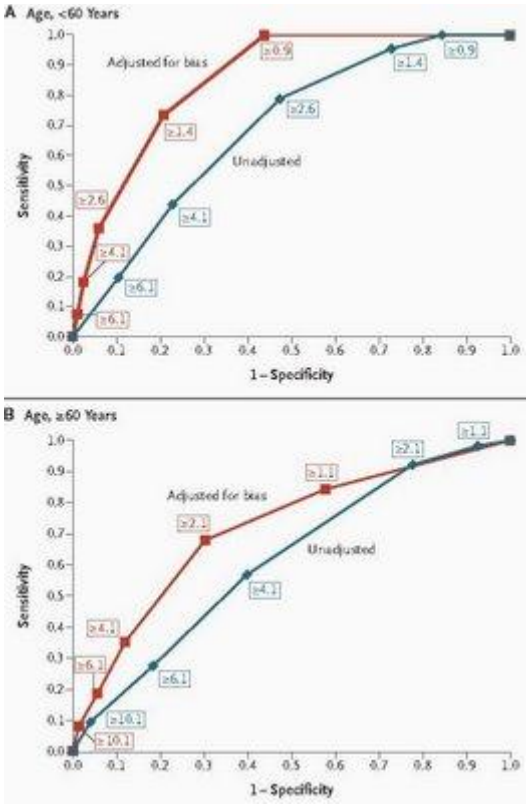
The PSA test is not just one test. It is not a black and white thing. It is a process that has evolved over time. There is not a good and bad PSA per se. Admittedly if you are 65 and

have a PSA of 60 you are in some trouble. But as we now know a PSA of 2.1 when you are 50 is of concern. But more critically the rate of change in PSA is almost diagnostic. Thus a 25% rate of increase per year should be followed up.

In July 2003 Punglia et al in the New England Journal of Medicine published a study which demonstrated that the then current set point for PSA missed many cancers. They stated:

"Adjusting for verification bias significantly increased the area under the ROC curve (i.e., the overall diagnostic performance) of the PSA test, as compared with an unadjusted analysis (0.86 vs. 0.69, P<0.001, for men less than 60 years of age; 0.72 vs. 0.62, P=0.008, for men 60 years of age or older). If the threshold PSA value for undergoing biopsy were set at 4.1 ng per milliliter, 82 percent of cancers in younger men and 65 percent of cancers in older men would be missed. A digital rectal examination that is abnormal but not suspicious for cancer does not affect the overall performance characteristics of the test….A lower threshold level of PSA for recommending prostate biopsy, particularly in younger men, may improve the clinical value of the PSA test."

They presented the following Figure:



The PSA test has been refined over the period of these studies, the PLCO Study, "Prostate, Lung, Colon, Ovary".

Now to issue two, Let us assume that a biopsy is performed. If a Gleason score of 7 is noted then you best have some attention paid, even a 6 is a problem. You have cancer! It will grow. It may very well kill you! That is if you do not die of something else. The problem is twofold; first, the doubling time of the cancer cells may be short, and second, the metastatic potential could be great. For Prostate cancer has the habit of metting to the bones, especially the spine. Does one want to take that risk?

The European study states the following protocol:

"We identified 182,000 men between the ages of 50 and 74 years through registries in seven European countries for inclusion in our study. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years. The primary outcome was the rate of death from prostate cancer. Mortality follow-up was identical for the two study groups and ended on December 31, 2006..."

The European trial is akin to a Fire House which uses an answering machine which it checks every three days to see if there is a fire. They then study the town with this Fire House and a town without a Fire House and discover that there is no difference in destroyed houses. Well one would perhaps think that having someone there to answer the phone when it rings and then immediately dispatching a fire engine would improve things.

Let me explain. PSA screening once every year, this is based upon a tumor doubling time of 3 months, a DRE and PSA are performed. If the PSA is measured as per Punglia statistic then we would use 2.6 for men under 60. Punglia states:

"These findings, as well as recent data from a randomized trial showing that prostate-cancer treatment improves disease-free survival, 28 indicate that reduction of the threshold PSA level at which biopsy is recommended to 2.6 ng per milliliter, at least in men under 60 years of age, may be reasonable."

Subsequent studies indicate that the added measurement of velocity or rate of change per year is also critical. Thus a 25% per year rate of change should be used as a way to seek an examination.

The American Group provides the following results:

"From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained….In the screening group, rates of compliance were 85% for PSA testing and 86% for digital rectal examination. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41 to 46% for digital rectal examination. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70)."

This American group was one with PSA at 4.0 and a second where PSA may or may not have been used as was a DRE. This is NOT a comparison of two distinct samples. The control group is a mix of anything and everything. Thus there are in my opinion two major faults;

First, the PSA numbers were set too high since we now know they should be set lower.

Second, the Control group was not the untested group as may be inferred, it was unlike the European study which alleges no treatment, and it was tested but just haphazardly.

Thus we have four groups:

Group 1 (American): PSA at 4.0 and DRE annually

Group 2: (American) PSA at 4.0 and DRE haphazardly

Group 3: (European) PSA at 4.0 but only once every 4 years

Group 4: (European) No screening

What is missing is what we now know to be the case. A PSA at 2.0 and an age dependent PSA with velocity measurements.

Thus our conclusion is that the Bayesian analysis, namely determining the probability of death given PSA measurements is or is not independent of the PSA measurement. We believe that the Bayesian approach of using screening at 2.0 under 60 and then testing

and addressing a malignancy will reduce the a posteriori mortality. The data assessing that hypothesis appears to bear that out.

The NY Times headline is confusing, and frankly in error. The study proved at best that the specific screening protocol did not result in longer lives. That has been known now for six years! The question is what protocol will prolong life. It is not that PSA does not work; it just does not work as it was being used ten years ago. This study only shows that.

The Times further states:

"In the European study, 48 men were told they had prostate cancer and needlessly treated for it for every man whose death was prevented within a decade after having had a PSA test. Dr. Peter B. Bach, a physician and epidemiologist at Memorial Sloan-Kettering Cancer Center, says one way to think of the data is to suppose he has a PSA test today. It leads to a biopsy that reveals he has prostate cancer, and he is treated for it. There is a one in 50 chance that, in 2019 or later, he will be spared death from a cancer that would otherwise have killed him. And there is a 49 in 50 chance that he will have been treated unnecessarily for a cancer that was never a threat to his life. Prostate cancer treatment can result in impotence and incontinence when surgery is used to destroy the prostate, and, at times, painful defecation or chronic diarrhea when the treatment is radiation."

Again that is not what the data says. The data shows that men were treated and did not die in either case. The two US cases are so overlapping that a bright line is not there and the European cases due to the longer time between screenings also merge to being identical. The statement about impotence and the like are scare statements since we know that if you have cancer and if we do not know the true level of malignancy then we just remove it, we don't want to be sued.

This leads to the final issue, genetic evaluation. Namely as we have discussed elsewhere we believe that genetic testing for predisposition, presence, staging, and prevention is slowly making progress. It is this effort which will eventually bear fruit.

In a 2005 paper in Science by Tomlins et al they state:

"A central aim in cancer research is to identify altered genes that play a causal role in cancer development. Many such genes have been identified through the analysis of recurrent chromosomal rearrangements that are characteristic of leukemias, lymphomas, and sarcomas (1). These rearrangements are of two general types. In the first, the promoter and/ or enhancer elements of one gene are aberrantly juxtaposed to a proto-oncogene, thus causing altered expression of an oncogenic protein. This type of rearrangement is exemplified by the opposition of immunoglobulin (IG) and T cell

receptor (TCR) genes to MYC, leading to activation of this oncogene in B and T cell malignancies, respectively (2). In the second, the rearrangement fuses two genes, resulting in the production of a fusion protein that may have a new or altered activity…"

Their conclusion is:

"The existence of recurring gene fusions of TMPRSS2 to the oncogenic ETS family members ERG and ETV1 may have important implications for understanding prostate cancer tumorigenesis and developing novel diagnostics and targeted therapeutics. Several lines of evidence suggest that these rearrangements occur in the majority of prostate cancer samples and drive ETS family member expression. "

Thus gene expression will be essential as a diagnostic tool. In a recent 2008 NEJM article by Zheng et al they state:

"Multiple SNPs in each of the five regions were associated with prostate cancer in single SNP analysis. When the most significant SNP from each of the five regions was selected and included in a multivariate analysis, each SNP remained significant after adjustment for other SNPs and family history. Together, the five SNPs and family history were estimated to account for 46% of the cases of prostate cancer in the Swedish men we studied. The five SNPs plus family history had a cumulative association with prostate cancer ... In men who had any five or more of these factors associated with prostate cancer, the odds ratio for prostate cancer was 9.46 …, as compared with men without any of the factors. The cumulative effect of these variants and family history was independent of serum levels of prostate-specific antigen at diagnosis...SNPs in five chromosomal regions plus a family history of prostate cancer have a cumulative and significant association with prostate cancer."

This further indicates that significant gene progress is being made.

The key fact to take from this exercise is that the results proved something which has some merit. It did not address the true question of what PSA testing if any can reduce mortality. It proved that there was no difference between two sets of PSA testing protocols. However as we have argued one would not have expected a difference. Furthermore the work done since this trial has begun has fine-tuned this testing. The true question will ultimately be a genetic question.

The New York Times[18] had an editorial on the prostate papers in NEJM[19] which we commented upon yesterday. The Times says:

[18] http://www.nytimes.com/2009/03/20/opinion/20fri3.html?_r=1&ref=opinion

[19] http://www.nejm.org/doi/full/10.1056/NEJMoa0810696

"The studies — one done in the United States, one in Europe — both show that screening had little or no effect in reducing prostate cancer deaths."

That is NOT what the papers said. They said that the protocols used to screen had little or no effect. NOT that "screening had little or no effect".

The question the researchers should have asked was:

"What level of PSA yields a positive result regarding the reduction of mortality?"

or even better:

"What level of PSA and what level of PSA velocity yields a positive result regarding the reduction of mortality?"

They did not ask that question. They asked the question:

"Does a PSA test of 4.0 threshold reduce mortality as compared to two sample groups."

Well, as we also said the American sample groups were both "tested" albeit not as frequently, and the European sample groups were for all purposes untested. Thus frankly the level was wrong, which was known since 2003 as in NEJM, in the paper by Punglia et al[20], which showed that a PSA of 2.3 was required to get reasonable levels! The 4.0 level was outdated for six years. No wonder there was no positive result, in addition to the samples used.

Consider if we did a test that said for women we screen for palpable breast lesions only larger than 4 cm in diameter. Then we would likely conclude that breast screening is ineffective since those screened and those not screened died at the same rate!

This demonstrates two issues:

First, the newspapers do not have the basic competence to read and report the facts. Words mean something and in this case lives hang in the balance.

Second, you may get answers to a question but it may very well be the wrong question. Ten years ago this may have been the right question, but we learned something. So does that mean we just continue a flawed study.

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[20] http://www.nejm.org/doi/full/10.1056/NEJMoa021659

7 CONCLUSIONS

In this paper we have provided a summary overview of PSA and its usefulness and then we have spent time looking at the many trials that have been conducted with PSA and looking at its efficacy. The problem with PSA is that it is in the midst of a massive political debate. The debate is one where with the changes in health care provisioning, namely the significant takeover of health care by the Federal Government, now accounting for almost one third of the population, and growing, the need to keep costs down drive medical care rather than providing for the patient. We have argued this extensively elsewhere.

We have addressed the following issues:

Is PSA a useful test? The answer clearly is yes but it has it problems. One would never use the PSA alone. Family history is often a more of a factor than PSA alone.

Are the Trials showing the limited use of PSA valid? We have shown that the trials, European and American, were fundamentally flawed. Although they were originally well focused, as we learned more about PSA we learned that the point at which one should perform follow up are variable are oftentimes should be done sooner at lower PSA values. The Trials used protocols that were 20 years old and new information was obtained including PSA velocity and percent free PSA.

Is PSA testing cost effective? This is the QALY issue, the cost effectiveness of the test measured in years of life saved. However given the uncertainty over indolent and aggressive cancers the determination is still at issue.

Is the PSA issue at a point of certainty that a policy can be developed and promulgated via a CER approach. The answer is clearly no. There is no consistent basis of agreement in the clinical research. Moreover there is no agreement scientifically as how best to grade PCa. After a biopsy we have at best the Gleason scoring system, albeit useful, it does not necessarily reflect the best modalities of treatment. Considerable research must still be done on the topic.

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