PSA EVALUATION METHODOLOGIES: A LOOK AT MULTIPLE ALTERNATIVES AND MAXIMUM LIKELIHOOD TECHNIQUES

Terrence P McGarty
Massachusetts Institute of Technology
Cambridge, MA

Abstract

In this paper we develop a maximum likelihood method to discriminate between benign prostates, PCa, PIN and BPH using data collected over long time horizons and using a systems model of prostate cell growth and PSA generation by cell type. The model allows for a sequential analysis over the long time horizon and it demonstrates the use of secondary data such as age, family history and race as well.

1 INTRODUCTION

Currently there are a few readily measurable factors which we can ascertain whether a patient has PCa or not. The use of PSA, PSA velocity and % Free PSA are three measures we often see used and when used they result in considerable debate. One of the issues is that the gold standard test, namely biopsy of the prostate, itself has substantial error in determining if PCa exists. The only true standard currently available is biopsy of the removed prostate. The latter gold standard is hardly one useful in clinical studies of patients with no overt signs upon normal evaluation.

We thus are looking at other measures for ascertaining patient status regarding the PCa presence. Clearly if we had a better understanding of cellular pathways and if in so understanding there were more useful markers which could be readily available, then perhaps we could have a more robust set of tests. However, lacking such, we are left with the tree measures and other exogenous variable such as age, family history, race. In this paper we use these factors as a means to ascertain the efficacy of various approaches to determining is the patient has PCa. This is not a staging approach, it is merely a monitoring effort, a screening effort, which could be used assuming that long term consistent data is available. The latter point is often a handicap since the assays used over some period of time are often highly variable in their results. We model this with a noisy measurement variable.

We thus analyze several various approaches with a primary focus on a systems approach. The systems approach is consistent with the Dougherty dictates which we try to adhere to, with predictability and reproducibility being the dominant ones. The system model we develop herein is a simple model based upon measurable parameters which can be validated by its predictable capacity. The approach is to view the resulting data such as PSA over time to be capable of providing, along with other data, more reliable metrics for assessing the potential for PCa.

The key risk in such a model is the ability to use measurable parameters across some wide base of patients. There is not reliable answer to this at the current time. Perhaps this is just a problem of "kicking the ball down the street" with solving one part of the problem by merely placing the uncertainty on another portion.

2 THE PROBLEM

We present a simple model of the problem herein. We look at the study but Punglia et al as a baseline upon which to understand the issue. We also look at the analysis we have performed regarding the probability of missing a PCa on a biopsy, which is not inconsequential.

Let us look at a simple version of Punglia model. We show this below:

	Test Positive	Test Negative	
Disease Positive	100	50	150
Disease Negative	50	250	300
	150	300	450

This simple model then gives the probabilities of Sensitivity as 100/150 and Specificity of 250/300. However we know that if there were a PCa, then depending on its size we would expect a P[Missing PCa] of 25% or somewhere in that range. The question then is how does one modify this Table to account for that. Punglia modifies it for verification bias, namely just filling in those who were tested but not biopsied in some rational manner. Punglia alleges used data predicated on patient statistics. The approach was unfortunately not detailed in the paper. We performed another analysis wherein we looked at using the Zhou analysis based on Begg and Greenes approach. The answers were dramatically different.

Now using the above we get a Sensitivity of 66% and a Specificity of 83%. But let us make a simple set of assumptions for this case. We will arbitrarily assume that the miss rate in the case where there is PCa is 40% and where there is "no PCa" say 10%. The Table changes as follows:

	Test Positive	Test Negative	
Disease Positive	130	20	150
Disease Negative	75	225	300
	205	245	450

Then we have:

Sensitivity = 130/150 = 87%
Specificity = 225/300 = 75%

	Punglia	Adjusted
Sensitivity	66%	87%
Specificity	83%	75%

This is a non-trivial difference. The test becomes much more sensitive. It loses some specificity but it more than makes up for sensitivity. Thus is if we were to place costs on a test and its follow up, the higher the sensitivity the better it is since we then end up treating the disease. Thus there is a need to better adjust the tests accordingly.

There are two fold elements in adjusting tests. First we desire a better test using PSA and its adjuncts. Second, we need a better way to assess the gold standard, and if no possible then adjust the data to reflect the known lack of accuracy as we have shown here.

3 ALTERNATIVES

There are many ways in which one may use the available data and then use it to ascertain the presence or absence of PCa. None have superb diagnostic characteristics as far as detections systems go. However we look at two classic approaches herein and we first introduce the systems model which we have not observed in any of the current literature. The three approaches are:

Systems Model: This is a model which looks at cell growth and the resulting markers that such cells produce. We can measure the markers such as PSA and we can ascertain experimentally all of the parameters in the model. As we have stated before, the risk is that the parameters in the model have so great a patient to patient variability that the ultimate model is of little use. However there is not adequate data at this time to make that judgment.

3.1 THE SYSTEM APPROACH

The systems model looks directly at the cell growth and the resulting process within cells to emit PSA into the blood stream for monitoring. We use a simple birth-death model as a first approximation for cell size.

3.1.1 Basic Systems Model

Let assume we have a certain number of benign prostate cells. For the purpose of further simplicity we shall focus on luminal and basal cells and for the further purpose we shall use a Goldstein model and assume that luminal are derived from basal and thus can be considered as one type. Thus we assume the prostate is a simply an organized collection of a single set of benign cells. Then we have:

$$\frac{dN_{Benign}(t)}{dt} = \lambda_{Benign} N_{Benign}(t) - \mu_{Benign} N_{Benign}(t)$$

$\lambda = Birth\ Rate$

$\mu = Death\ Rate$

$N = Number\ of\ cells$

Now if the cells are stable then we have birth and death rates equal. Death in this cases is by normal apoptosis and birth is mitosis. We must recall that even in mitotic growth the apoptotic process is such as to keep total cell numbers at constant levels. This in benign conditions we have:

$$N_{Benign}(t) = N_B(t) = N_B(t_0)$$

Now let us consider an amalgam of the following types of cells:

1. Benign
2. Cancer
3. PIN
4. BPH

Each has its own growth characteristics. Each has its own birth-death equations, measurable in vitro for example. Yet they may actually interact. For example PCa cells may cause increased apoptosis amongst Benign cells, pushing them aside for their own benefit. BPH may grow on top of normal cells, for in fact they are a basic extension thereto. PIN may also extend on top of Benign cells but just enlarging the prostate as would be seen with BPH but with cells confined to the glands but with differing characteristics. Thus we seek to have models which combine all. Birth and death rates may be dependent in some general way on each other. Thus we could in general posit:

$$\frac{dN_i(t)}{dt} = \left[\sum_{n=1}^{6} \lambda_i(N_1,...,N_6) - \mu_i(N_1,...,N_6)\right] N_i(t) + w_i(t)$$

where

$N_1 = Benign$

$N_2 = PCa$

$N_3 = PIN$

$N_4 = BPH$

Here we have added a random process, w, which we shall assume is Gaussian Wiener process with zero mean and some determinable variance. The birth and death rates are determinable via experimental analyses.

We shall consider some simple binary models for this analysis.

Now we also note that we can relate PSA and % Free PSA ("PFP") as functions of N, the number of specific cells. Let us consider this as follows:

$$PSA(t) = \sum_{n=1}^{6} psa_n N_n(t)$$

where

$psa_n =$ *the PSA per cell of type n in circulation*

and

$$PPP(t) = \sum_{n=1}^{6} pfp_n N_n(t)$$

where

$pfp_n =$ *the PFP per cell of type n in circulation*

Thus we measure PSA(t) and PFP(t) over some set of time intervals. A simple thought experiments indicates that we can see stable PSA and PFP if we have benign cells, subject to normal noise which we have included.

Let us now consider two cases.

Case I: Benign and PIN. Here we assume benign and PIN. The PIN is additional cell growth but not as extensive as say BPH. We have the following model:

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B] N_B(t) + w_B(t)$$
$$\frac{dN_{PIN}(t)}{dt} = [\lambda_{PIN} - \mu_{PIN}] N_{PIN}(t) + w_{PIN}(t)$$

where

$$\lambda_B - \mu_B = 0$$
$$\lambda_{PIN} - \mu_{PIN} > 0$$

Note that we stable Benign calls but a slowly growing PIN set of cells. And this yields for the exogenous measurements the following:

$$PSA(t) = psa_B N_B(t) + psa_{PIN} N_{PIN}(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PIN} N_{PIN}(t)}{N_B(t) + N_{PIN}(t)}$$

Now as we see more PIN cells we see a slowly increasing PSA, subject to noise, and we see a PPT also changing on a weighted basis. Yet if pfb is identical for both Benign and PIN then we see that PFP remains constant and high.

Case II: PCa: In this case we have benign and cancer cells. The same model as above but with some substantial modifications. We see this first as follows:

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B(N_{PCa}(t))] N_B(t) + w_B(t)$$
$$\frac{dN_{PCa}(t)}{dt} = [\lambda_{PCa} - \mu_{PCa}] N_{PCa}(t) + w_{PCa}(t)$$

where

$$\lambda_B - \mu_B > 0$$
$$\lambda_{PCa} - \mu_{PCa} >> 0$$

and

$$\frac{\partial \mu_B}{\partial N_{PCa}} > 0$$

This implies that we have a decreasing cell count of benign cells and an increasing and growing count of PCa cells. Thus when we calculate the following:

$$PSA(t) = psa_B N_B(t) + psa_{PCa} N_{PCa}(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PCa} N_{PCa}(t)}{N_B(t) + N_{PCa}(t)}$$

We see that the number of PCa cells are growing and at a rate in excess of and Benign cells, which are declining and that psa of PCa is much smaller than that of Benign cells as it the pfp of PCa, which is quite small as compared to benign cells. Thus with PCa we see PSA increasing and PFP decreasing.

Now the question we pose is how do we determine:

$$P\left[PCa \middle| PSA(s), PFP(s); s\varepsilon(t_0, t)\right]$$

This is a classic detection problem. We have solved that problem in our earlier work[1]. We will present the analytical approach here. Before continuing, however, we want to demonstrate what we know and what we have speculated:

We know the following from experiment and can validate from more experiments:

1. Cell growth follows the models we have depicted.
2. Growth rates are determinable from such factors as mitotic rates and other methods which are well known.
3. Cancer cells do push our benign cells through a variety of methods which are well understood.
4. The measurements we have determined are well documented and the average rates we use in the models are determinable from measurements.

We do not really know the following:

[1] See McGarty, Stochastic Systems and State Estimation, Wiley, 1974.

1. The functional characteristic of the increased death rate, and even birth rate, of benign cells dependent on the new PCa cells. There is the issue of the PCa cells absorbing nutrients from the Benign cells as well as the issue of reducing normal mitotic reactions.

3.1.2 Hypothesis Detection Model

The detection model can be defined as follows:

Hypothesis 0: Benign

$$PSA(t) = psa_B N_B(t)$$
$$and$$
$$PFP(t) = \frac{pfp_B N_B(t)}{N_B(t)}$$

And

$$\frac{dN_B(t)}{dt} = \left[\lambda_B - \mu_B\right] N_B(t) + w_B(t)$$
$$where$$
$$\lambda_B - \mu_B = 0$$

Hypothesis 1: PCa

$$PSA(t) = psa_B N_B(t) + psa_{PCa} N_{PCa}(t)$$
$$and$$
$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PCa} N_{PCa}(t)}{N_B(t) + N_{PCa}(t)}$$

and

$$\frac{dN_B(t)}{dt} = \left[\lambda_B - \mu_B(N_{PCa}(t))\right] N_B(t) + w_B(t)$$
$$\frac{dN_{PCa}(t)}{dt} = \left[\lambda_{PCa} - \mu_{PCa}\right] N_{PCa}(t) + w_{PCa}(t)$$
$$where$$
$$\lambda_B - \mu_B > 0$$
$$\lambda_{PCa} - \mu_{PCa} >> 0$$
$$and$$
$$\frac{\partial \mu_B}{\partial N_{PCa}} > 0$$

Thus we want to find a detector, maximum likelihood as an example, using:

$$P\left[PCa \middle| DataSet\right] = \frac{P\left[DatSet \middle| PCa\right] P\left[PCa\right]}{P\left[DataSet\right]}$$

3.1.3 Adequacy of Data in Model

We now take a brief look at what the effects of patient to patient variability would be in the model. As we said, there are measurable constants which we can ascertain and use in the model. There are two sets of the constants. The first set if the growth parameters and the second is the measurement parameters.

Let us consider the growth first. We assume that there is an average parameter and some variation about that average. We then ask how do we modify the model accordingly. This is a simple first order modification where the δ represent the zero mean variation of the measurement of the related variable with a variance σ associated with it as determined from the measurement data. Thus we have:

$$\frac{dN_B(t)}{dt}$$
$$= \left[\hat{\lambda}_B + \delta\lambda_B - \hat{\mu}_B + \delta\mu_B\right] N_B(t) + w_B(t)$$
$$= \left[\hat{\lambda}_B - \hat{\mu}_B\right] N_B(t) + \left[\delta\lambda_B + \delta\mu_B\right] N_B(t) + w(t)$$
$$= \left[\hat{\lambda}_B - \hat{\mu}_B\right] N_B(t) + u(t) + w(t)$$
$$where$$
$$\lambda_B - \mu_B = 0$$

This model then uses the uncertainty of the measurements as an added noise term, albeit correlated with the cell count. If the "noise" associated with the measurements is small with respect to the count itself then we can reasonably augment the overall system noise to include that level.

This is a first order approach to including the issue of measurement uncertainty of the underlying parameters.

We can do the same with the measurements:

$$PSA(t) = psa_B N_B(t) + psa_{PCa} N_{PCa}(t)$$
$$= (\hat{psa}_B) N_B(t) + \hat{psa}_{PCa} N_{PCa}(t) + \delta psa_B N_B(t) + \delta psa_{PCa} N_{PCa}(t)$$
$$= (\hat{psa}_B) N_B(t) + \hat{psa}_{PCa} N_{PCa}(t) + r(t)$$

Where we replace the uncertainty with an r(t) as we did above.

3.2 LOGISTIC ANALYSES

The logistic approach looks at the probability of PCa and its dependence on certain variables. For the purpose of this analysis we know that it depends on:

1. PSA Level
2. % Free PSA
3. Velocity of PSA
4. Age
5. First Degree Relatives Having PCa
6. Race

This in a simple logistic model we define:

$$ln\left[\frac{P[PCa]}{1-P[PCa]}\right]=\alpha+\sum_{n=1}^{6}\beta_i x_i$$

where

$x_1 = PSA\ level$

$x_2 = \%\ Free\ PSA$

$x_3 = PSA\ velocity$

$x_4 = Age$

$x_5 = First\ Degree\ Relatives$

$x_6 = Race$

As compared to the system model which is based upon verifiable constants and an clear underlying physical process and model, this is pure statistical conjecture. Here we will use volumes of data to attempt to ascertain the relationships. In logistic analysis the relationship is posited ab initio and there may or may not be any underlying physical relationship. We merely use the data and then from the data try to fit the constants based upon a clinical determination of the disease state.

3.3 CLASSIFICATION METHODOLOGIES

Classification approaches include such methods as clustering, principal component analyses, and other such methods. If we have say six measurables at our hand then we can collect a great deal of data with an assumed determination of PCa being absent or present. Then in this six dimensional space we can map out sectors which show how we could split the space into PCa and Benign space. We leave it to the reader to see the use of these techniques and refer them to the references at the end of this paper. As Dougherty so aptly states, the use of many classifiers are based solely upon the data and its characteristics and it devoid of any understanding of the inherent pathology.

4 A MAXIMUM LIKELIHOOD SYSTEMS CLASSIFIER

We can now use the systems model to develop a classifier. We start with a simple binary decision between two hypotheses; benign or PCa. We assume that the system can be delivered in a discrete time manner, which frankly we know. We will follow the approach in VanTrees for this analysis. Thus we have for the system:

$$N_B(k+1)=$$
$$N_B(k)+\left(\lambda_B(k)-\mu_B(k)\right)N_B(k)+w_B(k)$$

under H_0 *which is the hypothesis of benign*

and under this hypothesis we have

$N(k)=N_B(k)$

$$N_B(k+1)=$$
$$N_B(k)+\left(\lambda_B(k)-\mu_B(k)\right)N_B(k)+w_B(k)$$
$$N_{PCa}(k+1)=$$
$$N_{PCa}(k)+\left(\lambda_{PCa}(k)-\mu_{PCa}(k)\right)N_{PCa}(k)+w_{PCa}(k)$$

under H_1 *which is the hypothesis of PCa*

and under H_1 *we have*

$N(k)=N_B(k)+N_{PCa}(k)$

This is a model for a Markov process assuming the noise is independent and Gaussian and it has zero mean. The variance may be time or sample dependent. Note also that we may have to adjust the birth and death constants to reflect the time between samples.

Now what we measure is:

Under H_0 *we have:*

$$PSA(k)$$
$$= psa_B N_B(k)+n_{PSA,B}(k)$$

and

$$PFP(k)$$
$$=\frac{pfp_B N_B(k)}{N_B(k)}=pfb_B N_B(k)+n_{PFP,B}(k)$$

Under H_1 *we have:*

$$PSA(k)$$
$$= psa_B N_B(k)+psa_{PCa}N_{PCa}(k)+n_{PSA,Both}(k)$$

and

$$PFP(k)$$
$$=\frac{pfp_B N_B(k)+pfp_{PCa}N_{PCa}(k)}{N_B(k)+N_{PCa}(k)}+n_{PFP,Both}(k)$$

Here the n(k) is a measurement noise sequence reflecting both assay errors as well as variations from the base line estimates. What we use for the decision statistics are the above sets of variables. The difficulty would be that they are derived from the same data sequences, the N(k) sequences and thus are combinations of variables. Also we can simplify the PFP by normalizing it by volume, assuming that the cells are each of equal volume. Namely benign cells and PCa cell have essentially the same volume. Thus we can write the above measurements as a simplified linear model as follows:

Under H_0 we have:

$$PSA(k) = psa_B N_B(k) + n_{PSA,B}(k)$$

and

$$PFP(k) = pfb_B N_B(k) + n_{PFP,B}(k)$$

Under H_1 we have:

$$PSA(k) = psa_B N_B(k) + psa_{PCa} N_{PCa}(k) + n_{PSA,Both}(k)$$

and

$$PFP(k) = pfp_B N_B(k) + pfp_{PCa} N_{PCa}(k) + n_{PFP,Both}(k)$$

Where we use volumetric normalized values for PFP.

Now we want the probabilities of PSA and PFP for all ks. We can write[2]:

For H_0

$$p(PSA(k), PFP(k) | N(k)) = \tilde{N}(psaN(k), \sigma_{PSA}) \tilde{N}(pfpN(k), \sigma_{PFP})$$

and

$$p(PSA(k), PFP(k), N(k) | N(k-1)) =$$
$$\tilde{N}(psaN(k), \sigma_{PSA}) \tilde{N}(pfpN(k), \sigma_{PFP}) \tilde{N}((\lambda - \mu)N(k-1), \sigma_N(k))$$

Thus we have the joint conditional probability being all Gaussian with known means and we know that the N(k)s are themselves incrementally conditionally independent since we have a Wiener process and it is independent.

Now if we use the likelihood ratio we want the following:

Let

$$r_{PSA} = \begin{bmatrix} PSA(1) \\ \dots \\ PSA(n) \end{bmatrix}$$

$$r_{PFP} = \begin{bmatrix} PFP(1) \\ \dots \\ PFP(n) \end{bmatrix}$$

$$r = \begin{bmatrix} r_{PSA} \\ r_{PFP} \end{bmatrix}$$

These represent the received vectors. To define the likelihood ratios we then use these:

$$p(r | H_0)$$
$$= \int p(r | x, H_0) p(x | H_0) dx$$

But

$$p(r | x, H_0) = \prod_{n=1}^{N} p(r_n | x_n, H_0)$$

and

$$p(x | H_0) = \prod_{n=1}^{N} p(x_n | x_{n-1}, H_0)$$

And they are all normal with defined means and variances. We thus can pairwise deal with these. However the inclusion of noise on the cell count model adds a bit of complexity so we shall assume that it can be ignore in a first order approximation. Then we can easily determine the likelihood ratio parameters as follows:

For H_0

$$N_B(k+1) = N_B(k) + (\lambda - \mu) N_B(k)$$

and for non-uniform intervals we write:

$$N_B(k+1) = N_B(k) + (\lambda - \mu)\Delta(k) N_B(k)$$

where we have λ and μ normalized accordingly

$\Delta(k)$ then is the sample time difference

For the measurements we have:

$$PSA(k) = psa_B N_B(k) + n_{PSA,B}(k)$$

and

$$PFP(k) = pfb_B N_B(k) + n_{PFP,B}(k)$$

These are independent random variables driven by the underlying count. Note that the sampling time issues plays no part in this expression. Obviously we have the same for the other case of PCa.

It can easily be shown that the likelihood ratio, specifically the log likelihood ratio can be given as follows:

Choose H_0 if:

$$\sum_{n=1}^{N} [PSA(k) - psa_B \alpha_B \Delta(n) N_0]^2 + [PFP(k) - pfp_B \alpha_B \Delta(n) N_0]^2 >$$
$$\sum_{n=1}^{N} \frac{[PSA(k) - psa_B \alpha_{B,PCa} \Delta(n) N_0 - psa_{PCa} \alpha_{PCa} \Delta(n) N_0^{PCa}]^2}{\sigma_{PSA}^2}$$
$$+ \frac{[PFP(k) - pfp_B \alpha_{B,PCa} \Delta(n) N_0 - pfp_{PCa} \alpha_{PCa} \Delta(n) N_0^{PCa}]^2}{\sigma_{PFP}^2}$$

Now we can consider the issue of choosing between the four hypotheses; B, PIN, BPH, and PCa. Again we rely upon the treatment in VanTrees. The model follows directly from above.

[2] Note we use the notation N(a,b) as a normal or Gaussian distribution with mean a and standard deviation b.

Let the following be the hypotheses:

$H_0 = Benign$

$H_1 = BPH$

$H_2 = PIN$

$H_3 = PCa$

Then we create the following likelihood ratios:

$$\Lambda_{i,j}(r) = \frac{p(r|H_i)}{p(r|H_j)}$$

Then we can set up the decision regions based upon the following rules:

$$\Lambda_{0,1}(r)\begin{cases} < c_{0,1} : Choose\ H_0\ or\ H_2\ or\ H_3 \\ > c_{0,1} : Choose\ H_1\ or\ H_2\ or\ H_3 \end{cases}$$

$$\Lambda_{1,2}(r)\begin{cases} < c_{1,2} : Choose\ H_1\ or\ H_0\ or\ H_3 \\ > c_{1,2} : Choose\ H_2\ or\ H_0\ or\ H_3 \end{cases}$$

$$\Lambda_{2,3}(r)\begin{cases} < c_{2,3} : Choose\ H_2\ or\ H_0\ or\ H_1 \\ > c_{2,1} : Choose\ H_3\ or\ H_0\ or\ H_1 \end{cases}$$

$$\Lambda_{0,2}(r)\begin{cases} < c_{0,2} : Choose\ H_0\ or\ H_1\ or\ H_3 \\ > c_{0,2} : Choose\ H_2\ or\ H_1\ or\ H_3 \end{cases}$$

$$\Lambda_{0,3}(r)\begin{cases} < c_{0,3} : Choose\ H_0\ or\ H_1\ or\ H_2 \\ > c_{0,3} : Choose\ H_3\ or\ H_1\ or\ H_2 \end{cases}$$

$$\Lambda_{1,3}(r)\begin{cases} < c_{1,3} : Choose\ H_1\ or\ H_0\ or\ H_2 \\ > c_{1,3} : Choose\ H_3\ or\ H_0\ or\ H_2 \end{cases}$$

These then set out mutually exclusive decision regions. The details are in VanTrees. Generally we seek a binary decision between something and PCa. Knowing these regions we can quantitatively calculate the ROC related probabilities and we can choose the thresholds to maximize the ROC areas as has been suggested in the literature.

5 EXAMPLE

We now consider a simple example. This is one where we are looking at almost 20 years of data, some missing, and we then look at a binary hypothesis of B or PIN. Consider the data on the following patient:

Year	PSA(Alone)	Delta PSA	Delta/Yr PSA Abs	PSA Velocity 3-SampleTests	PSA Free	PSA on Free PSA	%Free PSA
Feb-93	0.62	-	-	-	-	-	
Mar-94	0.53	(0.15)	(0.09)	-	-	-	
Feb-95	1.50	1.76	1.01	-	-	-	
Jan-96	0.62	(0.53)	(0.98)	(0.02)	-	-	
Jan-97	0.70	0.13	0.08	0.04	-	-	
Apr-98	0.77	0.12	0.06	(0.28)	-	-	
Aug-99	0.95	0.31	0.14	0.09	-	-	
Jul-00	1.10	0.14	0.16	0.12	-	-	
Aug-00	1.10	-	-	0.10	-	-	
Oct-01	1.10	-	-	0.05	-	-	
Nov-02	1.30	0.19	0.19	0.06	-	-	
Nov-03	1.19	(0.08)	(0.11)	0.03	0.50	1.30	38%
Nov-04	1.53	0.30	0.32	0.13	0.50	1.53	33%
Nov-05	1.22	(0.19)	(0.33)	(0.04)	0.50	1.53	33%
Dec-06	1.60	0.35	0.34	0.11	0.50	1.53	33%
Nov-07	1.49	(0.06)	(0.12)	(0.04)	0.50	1.53	33%
Nov-08	1.49	-	-	0.07	-	-	
Nov-09	2.20	0.48	0.70	0.19	-	-	
Feb-10	2.10	(0.01)	(0.52)	0.06	0.70	1.53	33%
Feb-10	1.80	(0.00)	(2.03)	(0.62)	0.70	1.53	39%
May-10	1.70	(0.01)	(1.57)	(1.37)	0.70	1.53	39%
Oct-10	2.00	0.08	0.27	(1.11)	-	-	

We now use the test we had above. We must look at the underlying statistics.

1. Variance of both PSA and PFP are about a 25% standard deviation. Thus since both are the same these factors can be removed from the analysis.

2. The number of normal cells in a 40 cc prostate can be assumed to be 10 million. We assume that we can normalize cell numbers in millions so that a cell count of 10 is the equivalent of 10 million.

3. We can assume that a benign prostate of 40 cc has a base level in a 40 year old male is 0.5 and PFP is 35%.

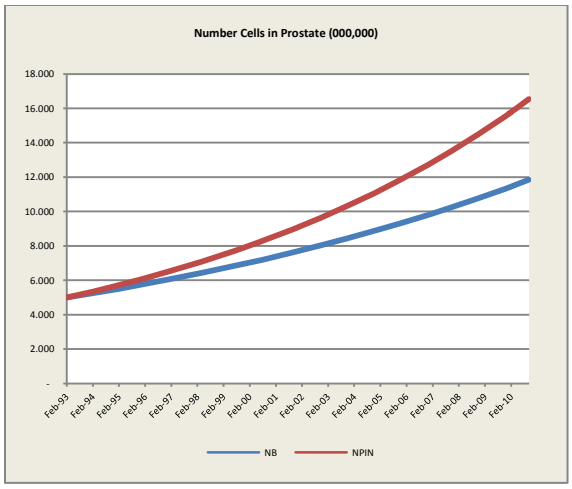
4. We can further assume that we have in a normal prostate a 25% increase in size per decade as the man ages over 50. Thus there is a 25% change. In contrast with BPH the doubling is every 5 years and for PIN we have every 7.5.

5. We assume that both BPH and PIN cells secret the same PSA and the binding is the same.

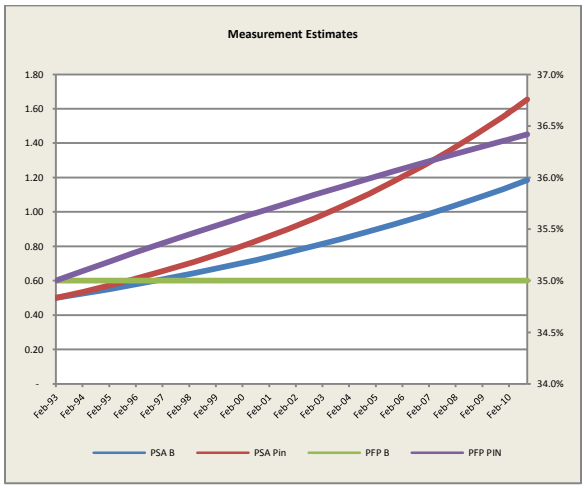
6. We assume that the doubling rate for cells with PCa is much shorter, namely 3 months and that PSA is the same per cell but PFP is 5% per cell not 35%.

The next issue is to establish a baseline for the incidence of any of these states, namely when do we measure X0. For simplicity we assume at 50 that all X0 are the same, based on a 40 year old baseline. This is one of the concerns with this model, namely establishing a baseline. We argue that similar estimation techniques can provide that as well.

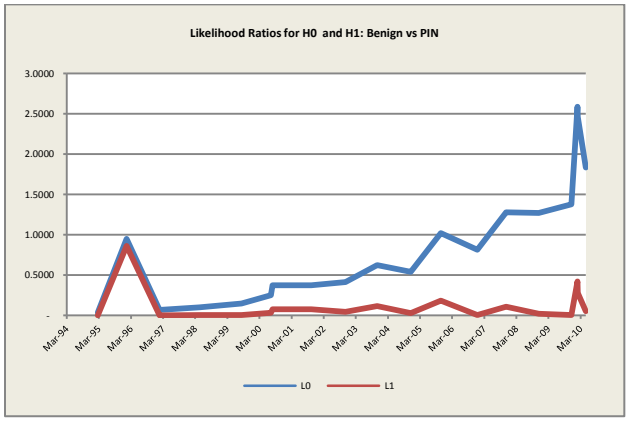
We now use this on the data we have shown earlier. First we show the call growth under two assumptions:



Then we show the projected measurement values to be used against the real measurements.



Then we show the likelihood ratios. Remember the selection is the smallest value based on it yielding the largest likelihood.



The interesting metric is the fact that we have a growing likelihood that the data suggests even five years earlier that PIN was present.

Thus we have shown that this maximum likelihood approach as modified appears to be readily applied and provides a strong suggestive set of guidelines for the physician.

6 BAYESIAN MODIFICATIONS

One can add substantial Bayesian modifications to this model in several dimensions. We consider two here:

Patient Characteristic: This is the use of age, sex, race, family history and the like to obtain finer estimates for discrimination purposes. There is some data available but the major problem is that fifteen and twenty year statistics on large cohorts is just not available at this time.

Patient Genetic Specifics: The recent work by Gudmundsson et al have provided an interesting set of insight into modeling PSA dynamics using SNPs from the patient and then ascertaining certain growth rates and production rates. Thus it is possible to choose these SNPs and determine the variable on finer grids for analysis. The data available at this time is inadequate to perform this analysis.

7 CONCLUSIONS

We have developed an alternative approach to the use of the limited data for assessing the risk of PCa in patients. It is an approach which is based upon the underlying dynamics of the cellular system and reflects the impact of key parameters of different cell growth rate and their impact on the measured variables. We have also shown that

1. The new metric requires a long period of collecting data on PSA and PFP. It then requires having reliable data on growth in the four differing scenarios. However it is interesting in that by including the data in this form we are effectively including velocity data implicitly.

2. The underlying constants may be based upon other factors as well, namely race, family history, and age. The Punglia paper does look somewhat at age segregation and recommends lower thresholds. We argue here that a running statistic may provide an improved discriminant.

3. ROC characteristics can be calculated analytically from this approach assuming certain constants.

4. The approach is direct and simple and seems to allow for early detection via a tracking of the likelihood ratio.

8 REFERENCES

1. Andriole, G., et al, Mortality Results from Randomized Prostate Cancer Screening Trial, NEJM, 2009 V 360 pp 1310-1319.

2. Augustin, H., et al, Prostate Cancers i the Transition Zone Part II, BJU Inter V 94 2004 pp 1226-1229.
3. Ayala, G., et al, High Levels of Phosphorylated Form of Akt-1 in Prostate Cancer and No Neoplastic Prostate Tissues are Strong Predictors of Biochemical Recurrence, Clin Can Res, V 10, 2004, pp 6572-6578.
4. Barry, M., Screening for Prostate Cancer among Men 75 Years of Age and Older, NEJM, 2008, V 359, pp 2515-2516.
5. Barry, M., Screening for Prostate Cancer, NEJM, 2009 V 360 pp 1351-1354.
6. Begg, C., R. Greenes, Assessment of Diagnostic Tests when Disease Verification is Subject to Selection Bias, Biometrics 1983 V 39 pp 207-215.
7. Bunz, F., Principles of Cancer Genetics, Springer(New York) 2008.
8. Campbell, A., L. Heyer, **Genomics, Proteomics, and Bioinformatics**, Benjamin Cummings (New York) 2003.
9. Carter, H., et al, Detection of Life Threatening Prostate Cancer With Prostate Specific Antigen Velocity During a Window of Curability, Jrl Nat Canc Inst, V 98, 2006, pp 1521-1527.
10. Carter, H., et al, Recommended Prostate Specific Antigen Testing Intervals, JAMA 1997, V 277, pp 1456-1460.
11. Catalona, W., et al, Prostate Cancer Detection in Men, JAMA, 1997 V 277, pp 1452-1455.
12. Cohen, R., et al, A Proposal on the Identification, Histologic Reporting, and Implications of Intraductal Prostatic Carcinoma, Arch Path Lab Med, V 131, 2007. pp 1103-1109.
13. Cronin, A., A., Vickers, Statistical Methods to Correct for Verification Bias, BMC Med Res Meth 2008 V 8 pp 2-9.
14. Dahia, P., PTEN, a Unique Tumor Suppressor Gene, Endo Rel Can, V 7 2000, pp 115-129.
15. Dahlman, A., et al, Effect of Androgen Deprivation Therapy on the Expression of Prostate Cancer Biomarkers, Pros Can and Prost Dis 2010 pp 1-7.
16. D'Amico AV; Schnall M; Whittington R; Malkowicz SB; Schultz D; Tomaszewski JE; Wein A. Endorectal Coil Magnetic Resonance Imaging Identifies Locally Advanced Prostate Cancer In Select Patients With Clinically Localized Disease. *Urology* 1998 Mar;51(3):449-54.
17. D'Amico, A., et al, Preoperative PSA Velocity and the Risk of Death from Prostate Cancer after Radical Prostatectomy, NEJM, V 351, 2004, pp 125-135.
18. DeMarzo, A., et al, Pathological and Molecular Aspects of Prostate Cancer, Lancet, V 361, 2003, pp 955-964.
19. Demichelis, F., et al, Distinct Genomic Aberrations Associated with ERG Rearranged Prostate Cancer, Gene, Chromo, Cancer, V 48, 1999, pp 366-380.
20. DeVita, V., et al, Cancer, Lippincott (Philadelphia) 2008.
21. Dougherty, E., Epistemology and the Role of Mathematics in Translational Science, To Be Published, Texas A&M.
22. Dougherty, E., et al, Epistemology of Computational Biology, Jour Bio Sys, V 14, 2006, pp 65-90.
23. Dougherty, E., et al, Validation of Computational Methods in Genomics, Curr Gen, V 8, 2007, pp 1-19.
24. Dougherty, E., On The Epistemological Crisis in Genomics, Current Genomics, V 9, 2008, pp 69-79.
25. Dougherty, E., Translational Science: Epistemology and the Investigative Process, Curr Gen, V 10, 2009, pp 102-109.
26. Duda, R., et al, Pattern Classification, Wiley (New York) 2001.
27. Ebersdobler, A., et al, Prostate Cancers in the Transition Zone Part I, BJU Inter V 94 2004 pp 1221-1225.
28. Epstein, J., G. Netto, Biopsy Interpretation of the Prostate, Lippincott (New York) 2008.
29. Ergun, A., et al, A Network Biology Approach to Prostate Cancer, Mole Sys Bio, V 3, 2007, pp 1-6.
30. Ernst, T., et al, Decrease and Gain in Gene Expression are Equally Discriminatory Markers for Prostate Cancer, Am Jrl Path, V 160, 2002, pp 2169-2180.
31. Esserman, L., et al, Rethinking Screening for Breast Cancer and Prostate Cancer, JAMA 2009 V 302 pp 1685-1692.
32. Esteller, M., Epigenetics in Cancer, NEJM, 2008 V 358 pp 1148-1159.
33. Feldman, B., D., Feldman, The Development of Androgen Independent Prostate Cancer, Nature Reviews Cancer, Vol 1, 2001, pp 34-45.
34. Figueiredo, M., et al, Advances in Preclinical Investigation of Prostate Cancer Gene Therapy, Am Soc Gene Therapy 2007 V 15 pp 1053-1064.
35. Foster, C., D. Bostwick, Pathology of the Prostate, Saunders (Philadelphia) 1998.
36. Freytag, S., Prostate Cancer Gene Therapy Clinical Trials, Am Soc Gene Therapy V 15 2007 pp 1042-1052.
37. Fukuhara, H., et al, Maximum Tumor Diameter, Pros Canc and Prost Dis 2010 V 13 pp 244-247.
38. Gardenes, J., et al, On the robustness of complex heterogeneous gene expression networks, Biophys Chem, 118 2005 pp. 225-228.

39. Garnick MB. Prostate Cancer Screening: Part I: The Screening Dilemma, Screening Tests and the Role of Prostate Specific Antigen Testing. Primary Care Reports. 2006; 12:1-12

40. Garnick MB. Prostate Cancer Screening: Part II: Treatment and Outcomes. Primary Care Reports. 2006; 12: 13-28

41. Goldstein, A. et al, Identification of a Cell of Origen for Human Prostate Cancer, Science, 2010 V 329, pp 568-571.

42. Grunkemeier, M, R. Vollmer, Predicting Prostate Biopsies, Ana Path 2006 V 126 pp 110-112.

43. Gudmundsson, J., et al, Genetic Correction of PSA Values Using Sequence Variants Associated with PSA Levels, Sci Transl Med V 2 Dec 2010, 62-92.

44. Gurel, B., et al, Molecular Alterations in Prostate Cancer as Diagnostic Prognostic, and Theraputic Targets, Adv Anal Path, V 15, 2008, pp 319-331.

45. Hanks GE, Hanlon AL, Pinover WH, Horwitz EM, Price RA, Schultheiss T. Dose selection for prostate cancer patients based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys*. 2000 Mar 1;46(4):823-32.

46. Hanley, J., B., McNeil, The Meaning and Use of the Area under a Receiver Operating Curve, Radiology 1982 V 143, pp 29-36.

47. Harmans, K., Unravelling of the Major Genetic Defects in Prostate Cancer, Doctoral Thesis, Erasmus Univ, Rotterdam, 2009.

48. Ho, J., et al, Comparative Effectiveness of Minimally Invasive vs Open Radical Prostatectomy, JAMA 2009 V 302 pp 1557-1564.

49. Hosmer, D., S., Lemeshow, Applied Logistic Regression, Wiley (New York) 2000.

50. Huang, H., PTEN Induces Chemosensitivity in PTEN-mutated Prostate Cancer, Jrl Bio Chem, V 276, 2001, pp 38830-38836.

51. Huang, S., et al, Blockade of NF-kB Activity in Human Prostate Cancer Cells is Associated with Suppression of Angiogenesis, Invasion, and Metastasis, Oncogene, V 20, 2001, pp 4118-4197.

52. Hunink, M., C. Begg, Diamond's Correction Method, A Real Gem or Just a Cubic Zirconium, Med Dec Making 1991 V 11 pp 201-203.

53. Iwarta, T., et al, Myc Overexpression Induces Prostatic Intraepithelial Neoplasia and Loss of Nkx3.1 in Mouse Luminal Epithelial Cells, Open Access, www.plosone.org ,V 5, 2010, pp e9427

54. Jaakola, L. et al, Expression of Genes Involved in Anthocyanin Biosynthesis, Plant Physiology, Vol 130 Oct 2002, pp 729-739.

55. Jaqmaspishvili, T., et al, Urine Markers in Monitoring Prostate Cancers, Pros Canc and Prost Dis, V 13, 2010, pp 12-19.

56. Jeet, V., et al, Modelling Prostate Cancer, Canc Met Rev, V 29, 2010, pp 123-142.

57. Kanamori, Y., et al, Correlation Between Loss of PTEN Expression and Akt Phosphorylation in Endometrial Carcinoma, Clin Can Res, V 7, 2001, pp 892-895.

58. Kantoff, P. et al, Prostate Cancer, Lippincott (Philadelphia) 2002.

59. Kim, H., X. Yang, Prevalence of High Grade Prostatic Intraepithelial Neoplasia and its Relationship to Serum Prostate Specific Antigen, Clin Uro, V 28, 2002, pp 413-417.

60. King, J., Cooperativity of TMPRSS2-ERG with PI3 kinase pathway Activation in Prostate Oncogenesis, Nature Gen, V 41, 2009, pp 524-526.

61. Kokontis, J., et al, Increased Androgen Receptor Activity and Altered c-myc Expression in Prostate Cancer Cells after Long Term Androgen Deprivation, J Can Res, V 54, 1994, pp 1566-1573.

62. Krubasik, P. et al, Expression and Functional Analysis of Gene Cluster Involved in the Synthesis of Decaprenoxxanthin reveals The Mechanism for c50 Carotenoid Formation, Eur J Biochem Vol 268 pp 3702-3708, Feb 2001.

63. Lawson, D., et al, Isolation and Functional Characterization of Murine Prostate Stem Cells, PNAS, 2007, V 104 pp 181-186.

64. Lawson, D., O. Witte, Stem Cells in Prostate Cancer Initiation and Progression, Jrl Clin Inves V 117 2007 pp 2044-2049.

65. Lawton CA; Won M; Pilepich MV; Asbell SO; Shipley WU; Hanks GE; Cox JD; Perez CA; Sause WT; Doggett SR; et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991 Sep;21(4):935-9.

66. Lawton CA; Won M; Pilepich MV; Asbell SO; Shipley WU; Hanks GE; Cox JD; Perez CA; Sause WT; Doggett SR; et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991 Sep;21(4):935-9.

67. Leite, K., et al, Repeat Prostate Biopsies Following Diagnoses of Prostate Intraepithelial Neoplasia and Atypical Small Gland Proliferation, Inter Brazil Jrl Uro, V 31, 2005, pp 131-136.

68. Lepor, H., R. Lawson, Prostate Diseases, Saunders (Philadelphia) 1993.

69. Li, J., et al, PTEN, a Putative Protein Tyrosine Phosphatase Gene Mutated in Human Brain, Breast, and Prostate Cancer, Science, V 275, 1997, pp 1943-1947.

70. Li, X., et al, NKX3.1 is Regulated by Protein Kinase CK2 in Prostate Tumor Cells, Mol Cell Bio, V 26, 2006, pp 3008-3017.

71. Lin, H., et al, Regulation of Androgen Receptor Signalling by PTEN, Mol Endo, V 18, 2004, pp 2409-2425.

72. Liu, A., et al, Correlated Alterations in Prostate Basal Cell Lauer and Basement Membrane, Int Jrl Bio Sci, V 5, 2009, pp 276-285.

73. Lu, Y., et al, A Bayesian Approach to Simultaneously Adjusting for Verification, Statst Med 2010 V 29, pp 2532-2543.

74. Lu-Yao, G., et al, Survival Following Primary Androgen Deprivation Therapy Among Men With Localized Prostate Cancer, JAMA, V 300 2008 pp 173-181.

75. Maira, S., et al, PI3K Inhibitors for Cancer Treatment, Biochem Soc Trans, V 37, 2009, pp 265-272.

76. Marcucci, G., et al, High Expression Levels of the ETS Related Gene ERG Predict Adverse Outcome, Jrl Clin Onc, V 25, 2007, pp 3337-3343.

77. McGarty, T. P, The Structure of the Upper Atmosphere, IEEE Automatic Control 1971.

78. McGarty, T., Health Care Policy, Telmarc Press (New York) 2009.

79. McGarty, T., **Stochastic Systems and State Estimation**, Wiley (New York) 1974.

80. McGarty, T.P., The PSA Controversy: Details, Models, Analysis and Recommendations, November 2010, MIT Working Paper.

81. McIntosh, M, N., Urban, A Parametric Empirical Bayes Method for Cancer Screening, Biostat 2003 V 4, pp 27-40.

82. McMenamin, M., et al, Loss of PTEN Expression in Paraffin-embedded Primary Prostate Cancer, Can Res, V 59, 1999, pp 4291-4296.

83. McNeil, B., J., Hanley, Statistical Approaches to the Analysis of Receiver Operating Curves, Med Dec Making V 4 1984 pp137-149.

84. Metzker, M., Sequencing Technologies, Nature Rev V 11, 2010, pp 31-46.

85. Mjolsness, E., et al Gene Regulation Networks with Signaling and Cell Division in Development Satiations, IEEE Biomed Engr Houston TX Oct 2002.

86. Mora, L., et al, Prostate Adenocarcinoma: Cellular and Molecular Abnormalities, Can Contrl, V 8, 2001, pp 551-561.

87. Mosquera, J., et al, Characterization of TMPRSS2-ERG Fusion in High Grade Prostatic Intraepithelial Neoplasia and Potential Clinical Implications, Clin Can Res, V 14, 2008, pp 3380-3385.

88. Mosquera, J., et al, Prevalence of TMPRSS2-ERG Fusion Prostate Cancer among Men Undergoing Prostate Biopsy in the United States, Clin Can Res, V 15, 2009, 4706-4711.

89. Nantermet, P., et al, Identification of Genetic Pathways Activated in Androgen Receptor during the Induction of Proliferation in the Ventral Prostate Gland, Jrl Bio Chem, V 279, 2004. pp 1310-1322.

90. Nelson, W. G., et al, Prostate Cancer, NEJM, V 349 N 4 July 2003, pp 366-381.

91. Oesterling JE; Martin SK; Bergstralh EJ; Lowe FC. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. *JAMA* 1993 Jan 6;269(1):57-60.

92. O'Shaughnessy, J., et al, Treatment and Prevention of Intraepithelial Neoplasia, Clin Cancer Res, V 8, 2002, pp 314-346.

93. Papatsoris, A., et al, The Power and Promise of "Rewiring" the Mitogen Activated Protein Kinase Network in Prostate Cancer Theraputics, Mol Can Ther, V 6, 2007, pp 811-819.

94. Partin, A., et al, Combination of Prostate Specific Antigen, Clinical Stage and Gleason Score, JAMA, 1997 V 277 pp 1445-1451.

95. Pecorino, L., Molecular Biology of Cancer, Oxford (New York) 2008.

96. Peng, C., et al, An Introduction to Logistic Regression Analysis and Reporting, Jrl Ed Res, V 96 2002 pp 3-9.

97. Pepe, M., The Statistical Evaluation of Medical Tests for Classification and Prediction, Oxford (New York) 2003.

98. Pollack A, Zagars GK, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol*. 2000 Dec 1;18(23):3904-11.

99. Prosnitz RG, Schneider L, Manola J, Rocha S, Loffredo M, Lopes L, DíAmico AV. Tamsulosin palliates radiation-induced urethritis in patients with prostate cancer: results of a pilot study. *IJROBP* (1999 Oct 1) 45(3):563-6.

100. Punglia, R., et al, Effect of Verification Bias on Screening for Prostate Cancer, NEJM, 2003 V 349, pp 335-342.

101. Radu, A., et al, PTEN Induces Cell Cycle Arrest by Decreasing the Level and Nuclear Localization of Cyclin D1, Mol and Cell Bio, V 23, 203, pp 6139-6149.

102. Roach M 3rd, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and

neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol*. 2003 May 15;21(10):1904-11.

103. Roach M, DeSilvio M, et. al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* (2003 May 15) 21(10): 1904-11.

104. Samaratunga, H., J. Epstein, What is the Molecular Pathology of Low Risk Prostate Cancer, World J Uro, V 26, 2008, pp 431-436.

105. Sanda, M., I. Kaplan, A 64 Year Old Man with Low Risk Prostate Cancer, JAMA, V 301, 2009, pp 2141-2151.

106. Sanguineti G; Agostinelli S; Foppiano F; Franzone P; Garelli S; Marcenaro M; Orsatti M; Vitale V. Adjuvant Androgen Deprivation Impacts Late Rectal Toxicity After Conformal Radiotherapy Of Prostate Carcinoma. *Br J Cancer* 2002 Jun 17;86(12):1843-7

107. Savli, H., et al, Gene Network and Canonical Pathway Analysis in Prostate Cancer, Exp Mol Med, V 40, 2008, pp 176-185.

108. Schnell. S, T. Turner, Reaction Kinetics in Intracellular Environments with Macromolecular Crowding, Biophys and Molec Bio vol 85 2004 pp. 235-260.

109. Schroder, F., et al, Screening and Prostate Cancer Mortality in a Randomized European Study, NEJM, 2009 V 360 pp 1320-1328.

110. Schroder, F., Progress in Understanding Androgen Independent Prostate Cancer, Euro Uro, V 53, 2008, pp 1129-1137.

111. Schroder, F., R., Kranse, Verification Bias and the Prostate Specific Antigen Test, NEJM, 2003, V 349, pp 393-395.

112. Schultheiss TE; Lee WR; Hunt MA; Hanlon AL; Peter RS; Hanks GE. Late GI and GU Complications in the Treatment of Prostate Cancer. *Int J Radiat Oncol Biol Phys* 1997 Jan 1;37(1):3-11)

113. Setlur, S., et al, Integrative Microarray Analysis of Pathways Dysregulated in Metastatic Prostate Cancer, Cancer Res, V 67, 2007, pp 10296-10303.

114. Sevli, S., et al, The Function of microRNAs, small but potent molecules, in Human Prostate Cancer, Pros Can and Pros Dis, V 13, 2010, pp 208-217.

115. Sharifi, N., et al, Androgen Deprivation Therapy for Prostate Cancer, JAMA, V 294, 2005, pp 238-244.

116. Shen, M., C. Abate-Shen, Roles of the Nkx3.1 Homeobox Gene in Prostate Organogenesis and Carcinogenesis, Dev Dynam, V 228, 2003, pp 767-778.

117. Sica, G., Bias in Research Studies, Radiology, 2006 V 238 pp 780-789.

118. Smith MR, Finkelstein JS, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2002 Feb;87(2):599-603

119. Styerberg, E., et al, Prediction of Indolent Prostate Cancer, Jrl Uro, 2007 pp 107-112.

120. Styerberg, E., et al, Prediction of Indolent Prostate Cancer, Jrl Uro, 2007, V 177, pp 107-112.

121. Su, L., Early Diagnosis and Treatment of Cancer: Prostate Cancer, Saunders(New York) 2010.

122. Swanson, K, et al, Prostate Specific Antigen, Am Jrl Clin Path, 2006, V 125 pp 331-333.

123. Swanson, K., et al, Prostate Specific Antigen, Am Jrl Path 2006, pp 331-333.

124. Taylor, B., Integrative Genomic Profiling of Human Prostate Cancer, Cancer Cell, V 18, 2010, pp 1-12.

125. Theodoridis, S., K., Koutroumbas, Pattern Recognition, Academic (New York) 2009.

126. Thompson, I. et al, Operating Characteristics of Prostate Specific Antigen, JAMA 2005 V 294 pp 66-70.

127. Thompson, I., et al, Assessing Prostate Cancer Risk, Jrl Nat Cancer Inst V 98 2006 pp 529-534.

128. Tobias, A., Directed Evolution of Biosynthetic Pathways to Carotenoids with Unnatural Carbon Bonds, PhD Thesis, Cal Tech, 2006.

129. Tomlins, A., ETS Rearrangements and Prostate Cancer Initiation, Nature, V 448, 2007, pp 595-599.

130. Tomlins, S., et al, Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer, Science, V 310, 2005, pp 644-648.

131. Turing, A., The Chemical Basis of Morphogenesis, Phil Trans Royal Soc London B337 pp 37-72, 19459.

132. Turner, D., The Role of ETS Transcriptional Regulation in Hormone Sensitive and Refractory Prostate Cancer, Open Can Jrl, 2010, V 3, pp 40-48.

133. Tuxhorn, J., et al, Reactive Stroma in Human Prostate Cancer, Clin Cancer Res V 8 2002 pp 2912-2923.

134. Van Trees, H. L., **Detection Estimation and Modulation Theory**, Wiley (New York) 1968.

135. Vicini FA, Abner A, Baglan KL, Kestin LL, Martinez AA. Defining a dose-response relationship with radiotherapy for prostate cancer: is more really better? *Int J Radiat Oncol Biol Phys*. 2001 Dec 1;51(5):1200-8.

136. Vliestra, R., et al, Frequent Inactivation of PTEN in Prostate Cancer Cell Lines and Xenografts, Can Res, V 58, 1998, pp 2720-2723.

137. Vogelstein, B., K., Kinzler, Cancer Genes and the Pathways They Control, Nature Med, V 10, 2004, pp 789-799.

138. Vohradsky, J., Neural Network Model of Gene Expression, FASEB Journal, Vol 15, March 2001, pp. 846-854.

139. Vollmer, R., Predictive Probability of Serum Prostate Specific Antigen for Prostate Cancer, Am Jrl Clin Path, 2006 pp 336-342.

140. Vollmer, R., Predictive Probability of Serum Prostate Specific Antigen for Prostate Cancer, Am Jrl Clin Path 2006 V 125, pp 336-342.

141. von Knobloch, R., et al, Genetic Pathways and New Progression Markers for Prostate Cancer Suggested by Microsatellite Allelotyping, Clin Can Res, V 10, 2004, pp 1064-1073.

142. Walsh, P., et al, Localized Prostate Cancer, NEJM, V 357, 2007, pp 2696-2705.

143. Wang, X, et al, Notch-1 Expressing Cells are Indispensible for Prostatic Branching Morphogenesis, Jrl Bio Chem, V 279, 2004, pp 24733-24744.

144. Wang, X., et al, A Luminal Epithelial Stem Cell That is a Cell of Origen for Prostate Cancer, Nature 2009 V 461 pp 495-500.

145. Watson, D. et al, ETS Transcription Factor Expression and Conversion During Prostate and Breast Cancer Progression, Open Access Cancer Journal, 2010, pp 24-39.

146. Weber DC; Bieri S; Kurtz JM; Miralbell R. Prospective Pilot Study of Sildenafil For Treatment of Postradiotherapy Erectile Dysfunction In Patients With Prostate Cancer. *J Clin Oncol* 1999 Nov;17(11):3444-9.

147. Weinberg, R., The Biology of Cancer, Garland (New York) 2007.

148. Wolf, D., et al, Transcriptional Down Regulation of c-myc in Human Prostate Carcinoma Cells by the Synthetic Mibolerone, Br Jrl Cancer, V 65, 1992, pp 376-382.

149. Yemelyanov, A., et al, Tumor Suppressor Activity of Glucocortoid Receptor in the Prostate, Oncogene, 2006, pp 1-12.

150. Zelefsky MJ, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys*. 1998 Jun 1;41(3):491-500.

151. Zelefsky MJ; McKee AB; Lee H; Leibel SA. Efficacy of Oral Sildenafil In Patients With Erectile Dysfunction After Radiotherapy For Carcinoma Of The Prostate. *Urology* 1999 Apr; 53(4):775-8.

152. Zhang, L. et al, NF-kB Regulates Androgen Receptor Expression and Prostate Cancer Growth, Am Soc Invest Path, V 175, 2009, pp 489-499.

153. Zhou, X., et al, Statistical Methods in Diagnostic Medicine, Wiley (New York) 2002.

154. Zietman AL, Prince EA, Nafoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi in vitro tumor system. *Int J Radiat Oncol Biol Phys* (1997 Jul 15) 38: 5: 1067-70.

155. Zong, Y., et al, ETS Family Transcription Factors Collaborate with Alternative Signalling Pathways to Induce Carcinomas from Adult Murine Prostate Cells, PNAS, V 106, 209, pp 12465-12470.