Controllable Diseases: A Study in Pre-emption

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1 INTRODUCTION

In our prior White Papers we have looked at the Health Care System as a totality and then we looked at preventable diseases in some detail, namely Type 2 Diabetes. In this paper we look at remediable disease, specifically a set of cancers.

There are certain pre-conceived assumptions that we have seen over and over again permeating the plans and proposals. These are mind sets, world views that seem to restrict what can be achieved as well as what can be done. We use this analysis as a means to highlight them and then to address how they can be reset to reveal alternative and improved paths of progress.

Many of the assumptions made by the analysts and policy makers in Health Care are akin to what would be done a century ago where we would be concerned about TB and infectious diseases. At that time they were growing in incidence and were causing major problems in the area of public health. If one made health care decisions based on extrapolating that world sans antibiotics and expanding public health then the results would also have shown catastrophic results. We argue herein that there is a major change occurring in the field of controllable diseases like major cancers.

This means that it may be possible to intervene early, as we are seeing with prostate, breast, melanoma, and other cancers and take remedial action. The next step is to do so earlier using genetic markers. Thus it is anticipated that in the next ten years we may readily find the genetic markers for major cancers, not cures, but predispositions and also markers relating to specific treatments. We argue that if we look forward into a world with these changes then we can readily look at developing heath care policy with a forward look hopefully more consistent with the reality we are to face.

1.1 ASSUMPTIONS

The major fact about so many policy types is that they predicate their forward looking plans and dicta on past processes, procedures and knowledge. This can be a fatal and costly error. Medicine is at the precipice of a massive change in the delivery of healthcare as a result of the introduction of genetic methods for assessing the potential, diagnosing the presence, staging the disease, and eventually curing the disease. This means that the past is not a prolog to the future by mere extrapolation. The policy makers work under assumptions based upon past paradigms.

Let us set out some of these assumptions.

1. **Healthcare Demand is independent of cost.** This means that people are impervious to the costs that result in bad health. We know that this is not the case all one must do is look at the statistics of smoking. In the states with the largest taxes the numbers of smokers has declined the greatest. The same we have argued can be accomplished with the obesity issue. We also argue that the same may be achievable with the issues relating to controllable diseases. Demand we believe can be modulated with economic incentives and penalties.

2. **The Diseases today are the diseases of tomorrow**. Thirty five years ago no one heard of HIV. Then it became a pandemic and now it is a controllable disease. Cervical cancer caused by papilloma virus can now be prevented. Many of the kinase activated hematological cancers can be controlled by kinase inhibitors. This disease may go from terminal to chronic. Undoubtedly the mortality and morbidity tables will change as we deal with one disorder after another.

3. **The treatments today are linearly projectable into the future**. This means that we will continue to use surgical and pharmaceutical means to deal with disease states and that for certain acute and significant disease states we shall continue to rely upon massive hospitalizations as we have seen grow during the latter half of the 20th century. The reality may very well be different. The treatment of disease, especially cancers, may be addressed by genetic medications, by effecting blockage of the growth of tumors and by the actual elimination of them.

4. **The diagnostic tools we use today are linearly projectable into the future**. What do we mean here? This means that we continue to use say X-rays MRI and CAT in mammography for the detection of breast cancer. That BRCA genes are limited to a few people and that there will be no major breakthrough in this area in early detection. It means in prostate cancer that PSA and ultrasound approaches will continue with high false alarm rates and excess procedure and that also genetic markers will be used in a limited manner. There development of genetic markers is slowly evolving into a diagnostic tool which can replace many of those we use from normal metabolic testing. However it will take time to identify and standardize them.

5. **Staging of Cancers will continue to progress Using Criteria of metastasis and lymph node involvement**: Again, staging of cancers is performed to assess treatment and to determine possible issue of survival. The staging criteria are based upon large sets of past data. However as is becoming quite clear the individual genetic makeup of the cancer cell, a clone in almost all cases, dictates the progression of the disease much better than gross statistics. In fact the ability to assess the genetic profile of the malignancy should in time be the sine qua non as regards to assessing both treatment and survivability.

6. **Treatments will be based upon generally accepted staging criteria**. This is a major concern for many cancers have almost individual characteristics albeit the same staging

criteria may be met. Take prostate cancer for example. In a 70 year old male, with a PSA of 6.0, a rate of increase of say 35% per annum in PSA and no palpable node, upon an ultrasound it is found that there are potential cancerous lesions. The Gleason grade is 6 in all sections. Thus what should be the treatment? A recent New England Journal of Medicine question gave an answer to a similar question almost equally divided between watchful waiting, surgery and implants. Specifically, *"Among the 3720 votes cast, 29% were for expectant management, 33% for radiotherapy, and 39% for radical prostatectomy."* It is amazing to consider that given several gross tests that the answers are so widely spread. It is not unlikely however that physicians and patients, having a choice, will select one which meets their own preconceived world views. The facts are twofold here. First the presence of certain genes, SNPs, gives a predisposition to prostate cancer and having a family member of first degree increases the risk tenfold. That is the predisposition element. It is not predictive. Then after a cancer is diagnosed the genes which the cancer cell itself expresses is a determinant for how aggressive it will be. Clearly not enough is known now as to what the best markers are and further even less is known why those markers are significant in the aggressiveness of the lesion. However, going from the above NEJM example to having markers, one could then make a much more rational decision about watchful waiting versus prostatectomy.

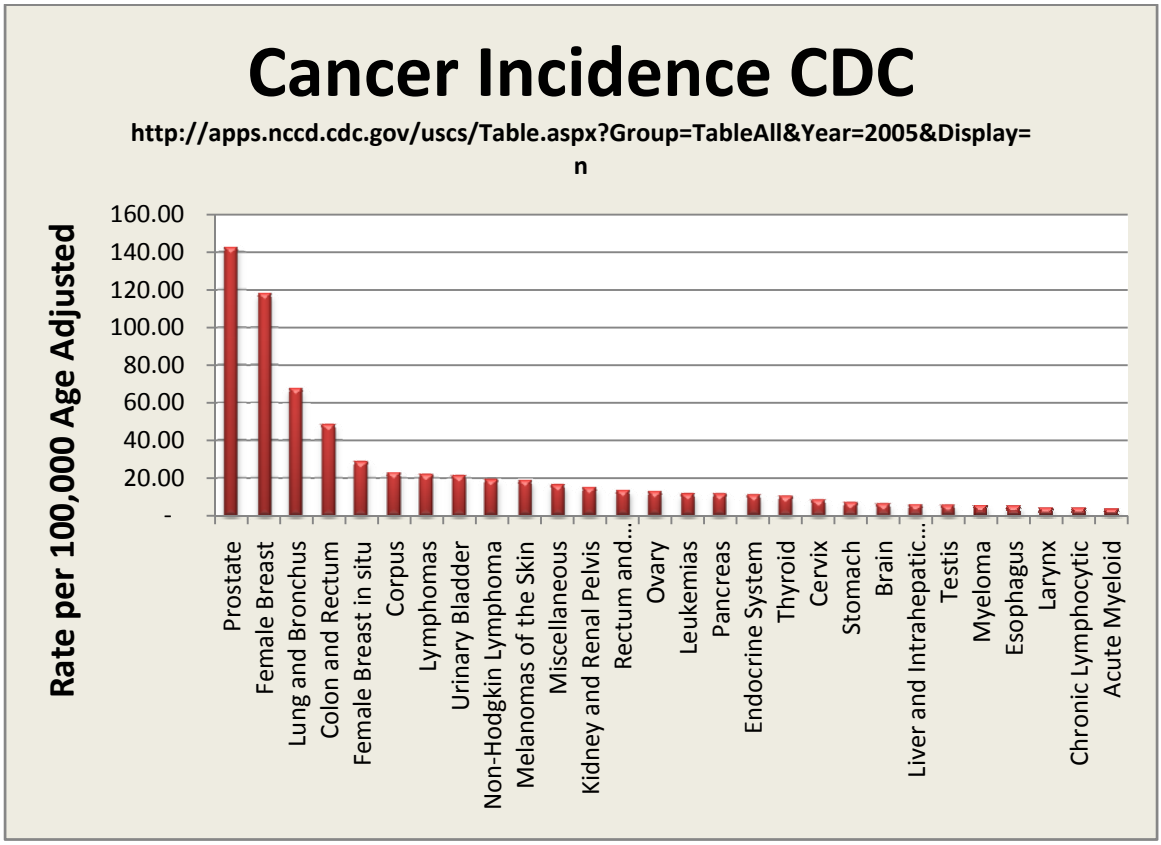
These assumptions must be extensively re-examined, they will not hold and the projections made from them and the policies developed based upon them are subject to failure. That failure will be quite costly.

1.2 BASIC INCIDENCE

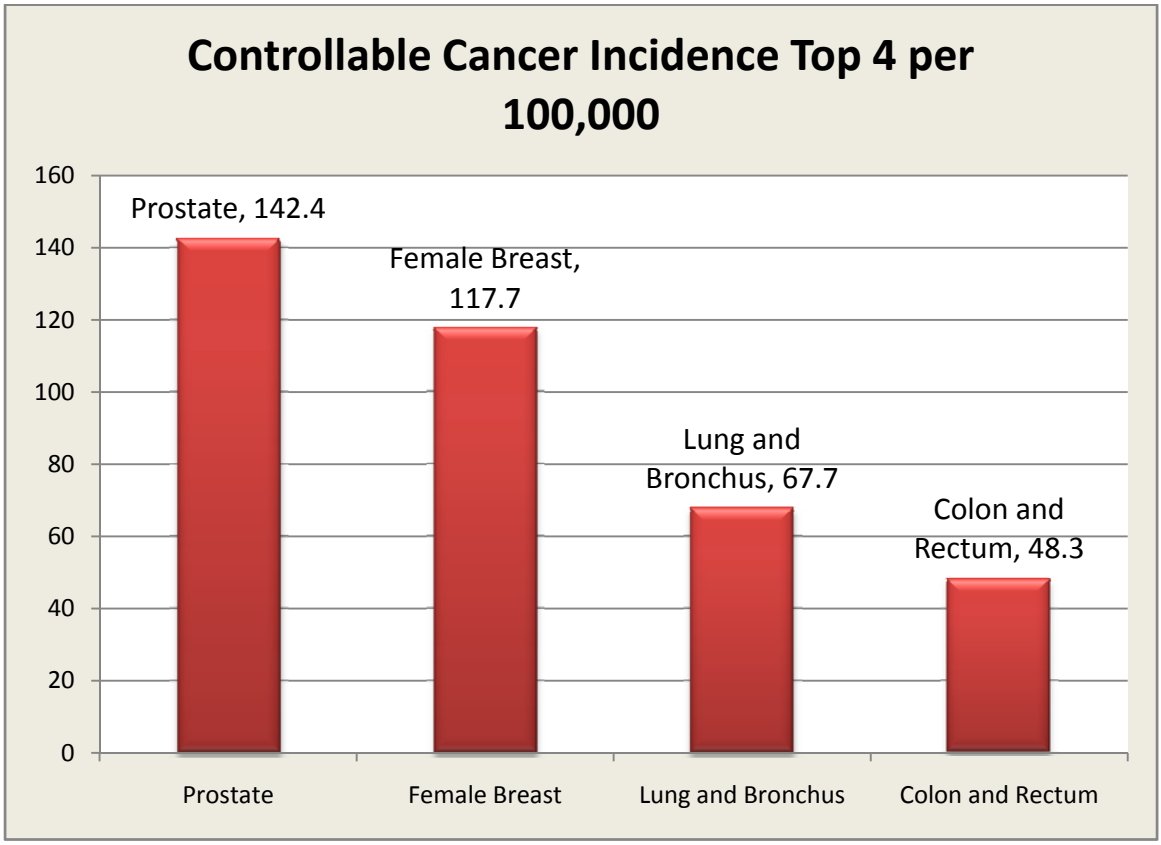
The past is not prolog to the future in health care. It may provide an understanding of where we may not have acted most effectively bit it is not a deterministic path that we must try to optimize our expenditures. It is a dynamic stochastic process with some form of reasonable albeit random perturbations imposed upon it.

We briefly review the CDC data on cancer incidence[1]. The following Figure depicts a broad base of cancers and their incidence. It is quite clear that lung, breast, prostate and colon dominate. Lung is almost totally controllable via cessation of cigarette smoking. The evidence of that is now overpowering. The other three are controllable by tools existing today. PSA and DRE are now accepted tools for prostate cancer, colonoscopy for colon cancer and mammography for breast cancer. They do not prevent the cancers but they allow for early detection and remediation or control of the cancer is a much less costly manner. The incidence of this cancer will not change.

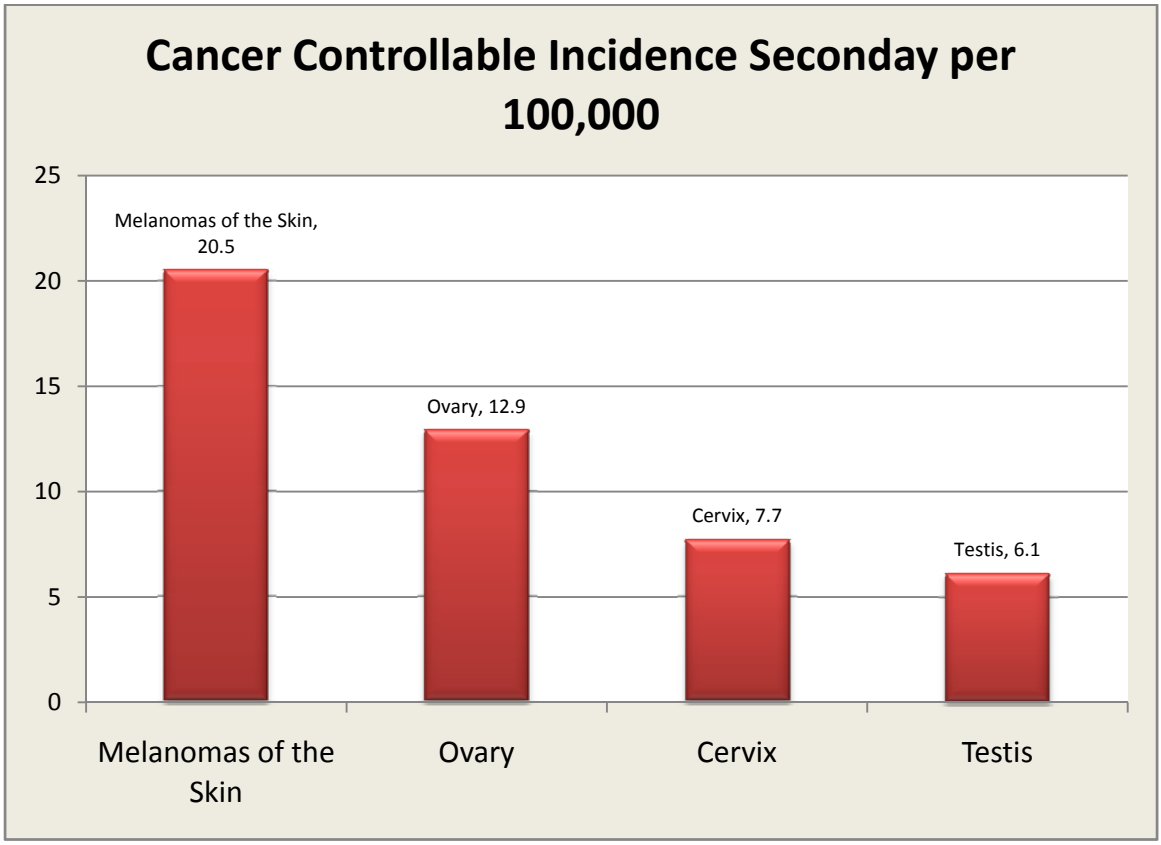
[1] See http://apps.nccd.cdc.gov/uscs/Table.aspx?Group=TableAll&Year=2005&Display=n



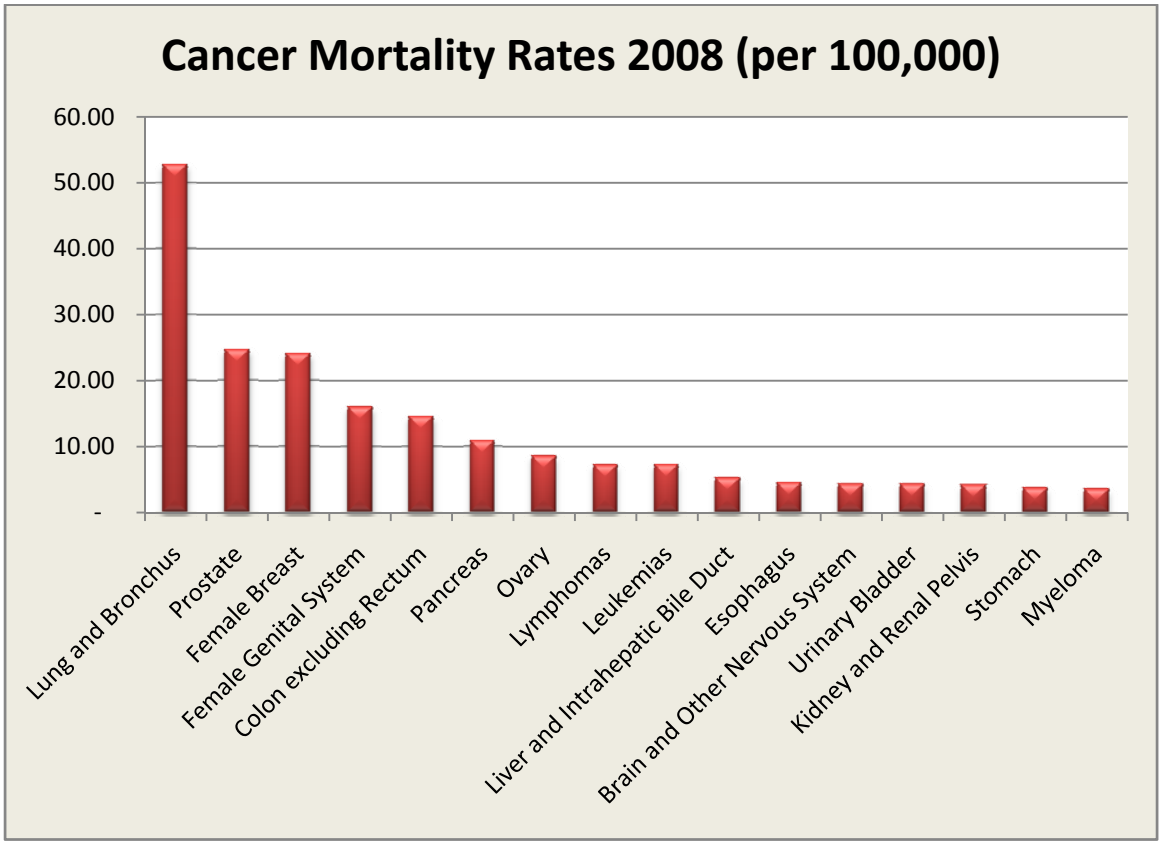
The following two Figures focus on eight cancers, the top four cancers and four other cancers. The other four are ovary, testis, melanoma, and cervix. In a sense all of these are also controllable, albeit at a cost ranging from low to high. Melanoma is an example of a controllable cancer. There is a genetic and environmental pre-disposition and if screened semi-annually, removal of superficial spreading malignant melanoma can result in reduced costs and dramatically reduced mortality and morbidity.



In the above it should be noted that lung cancers are for both male and female whereas prostate is male and breast is female. The incidence is per 100,000 of the group. Thus prostate and breast is for male and female only and it is not an incidence for all. Thus the total incidence of prostate is about 70 per 100,000 total population and the same for breast as 68 per 100,000 of the total. There is a small incidence of male breast cancer.



The following are the mortality rates for the cancers discussed above. Note that the same top three of lung, breast and prostate dominate.



1.3 MECHANISMS OF CONTROLLABILITY

The next issue is how these diseases can be controllable. The following table depicts the selected cancers and the detection methods which are of current use. They are all controllable but at a cost. For example colon cancer requires a colonoscopy, after baseline, of once every five years at a cost in 2008 dollars of $1500. This is $300 per annum and at this rate an extremely high percentages of colon adenomas can be detected before becoming metastatic and spreading and being removable at the time of colonoscopy. The costs are really in having adequate trained endoscopist.

The other extreme is ovarian cancer. This is a quite uncommon cancer with the incidence peaking at 70 years of age. It can be detected with transvaginal ultrasounds and CA125 testing every three months at the cost of $400 per visit or $1600 per year. The incidence is significantly lower than colon cancer and the resulting cost per detected even is more than two orders of magnitude higher. In addition the effectiveness of the screening still has some lack of specificity.

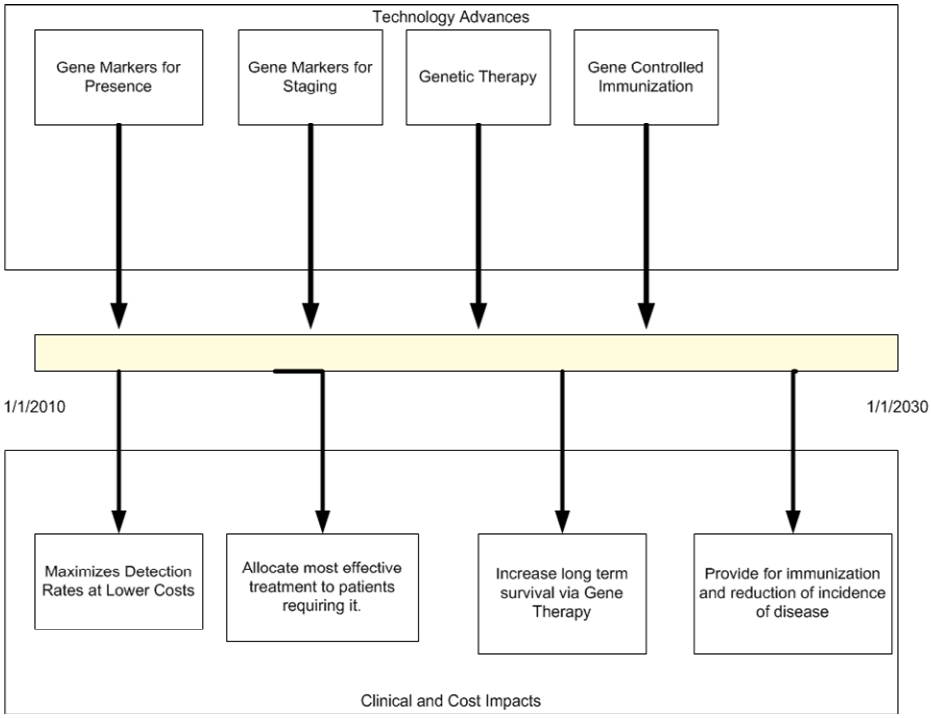
Disease	Detection	Controllability	Cost per year
Prostate	PSA, DRE annual	Removal	$250
Breast	Mammography annual	Removal	$350
Lung	X-Ray/Smoking	NA	0
Colon	Colonoscopy every 3-5 years	Removal	$300-500
Melanoma	Skin Exam Semiannual	Removal	$150
Ovary	Trans Vaginal Ultra, Quarterly, CA125	Removal	$1200
Cervix	Pap Smear annual	Excision	$200-300
Testis	Examination annual	Removal	$125

The above Table represents what is available in the current practice of medicine. The procedures provide varying degrees of sensitivity and specificity. Studies on ovarian cancers have shown variations in specificity which may result in unnecessary removal of ovaries. Colon cancer has shown that there is some lowered sensitivity on the ascending colon from a Canadian study but we have argued elsewhere that the Canadian study has flaws. The Pap smear has been a stand by and gold standard for years.

1.4 PROPOSED TIME/EVENT PATH

As we have discussed earlier, we see that there is a set of in going assumptions that policy makers and the like make regarding health care. In this section we attempt to break those assumptions. If one is to look at health care from 2010 through 2050 there will most likely be fundamental changes in not only the delivery of what is done now, but fundamental change in what health care is, driven by the changes in genetic diagnosis and treatment. Cancer, especially the one we consider here as well as the hematological ones will have been greatly impacted upon by these changes.

Consider the twenty year time line we have drawn below. There are four steps we anticipate and consequences from both.



The following are the steps:

1. **Gene Markers for Presence**: There has been a tremendous amount of work performed in all of the eight target cancers for gene markers for a predisposition for the cancers. Clearly having a gene is not totally predictive but it permits a measure for increasing vigilance and testing. Thus have a set of gene markers for cancers which can be remediated are quite useful. It does not stop the gold standard test of pathological resection. There as of yet does not appear to be a large set gene markers for presence. We know that the BRCA gene establish a high probability for breast and other cancers. However they in and of themselves do not establish presence. However we know that when a clonal cancer starts there will be the results of both primary and secondary pathways on the clonal cells themselves as well as other cells reacting to the clonal aberration which can be measured and used to detect presence.

2. **Gene Markers for Staging**: Gene markers for staging are the next step. This means that we can now, having detected the presence of the cancer, determine its aggresivity and then to take the appropriate actions. Prostate cancer is typical in this class. Some colon cancers also fall here as do some limited superficial spreading malignant melanomas. In fact it is know that certain melanomas regress, albeit may latter appear as a secondary met.

3. **Genetic Therapy**: There is a beginning effort in gene therapy now. It is slow and is progressing along the usual lines. However in the next twenty years this is expected to grow at a startling rate. This will be a case of many small victories until the tools are

developed and then a massive growth phase. This will dramatically reduce the morbidity and mortality. The issue is will it reduce the costs. Again with Federal funding and rights accruing to the sponsors such costs may be minimized.

4. **Genetic Immunization**: This is the final step in the time horizon we are looking at. Clearly there will be a way to establish what we see as an immunization. This is not akin to the cervical cancer immunization against the papilloma virus but an actual genetic insertion or modification to either repair or block the effects of the precipitating genes.

These four are also benchmark elements for policy formulation and Government funding. The basic research is completed to permit much of this to commence, albeit there are still some loopholes to be filled in, but a focused research program will be essential to remediate the cancers we have discussed herein. If this is done, then a forward looking plan, one looking at remediation of controllable diseases via genetic means will evolve and become an integral part of any long range health care plan. It is not just a question of who pays what for what is currently performed. This is an event changing program

2 GENETIC IMPLICATIONS

Cancer is a disease of lack of genetic control. The human body has cells which are reproducing continuously. Red blood cells replenish themselves every 90 days or sooner. The skin, and other epithelial tissues are being lost and being replenished. The cycle of creation and cell death, apotosis, is ongoing and as part of that is the conversion od DNA from one cell to the new cells. Some times that does not work for a variety of reasons. This results in but a single cell going awry. Most of the time it is managed by the immune system which recognizes self from non self. Every once in the while it does not work and a clonal cancer cell explodes into full blown cancer.

2.1 CURRENT UNDERSTANDING

Thus to understand Cancer we must understand the genetics of this disease. Foulkes has recently reviewed the genetic factors in cancers. His summary of the major forms are detailed as follows:

Lung cancer: "Lung *cancer is mainly attributable to tobacco use, and few large families with multiple cases of lung cancer are suitable for linkage analysis. Even if such families were available, it is not obvious that a single gene with a large effect would account for the cases observed. Nevertheless, one locus on chromosome 6q has been suggested by a traditional linkage study, though no gene has yet been identified. Some tumor-suppressor genes are associated with substantial increases in the risk of lung cancer, and in persons carrying mutations in these genes; tobacco smoking may be particularly dangerous. For example, in families with the Li–Fraumeni syndrome, smokers who carry a TP53 mutation are at much higher risk for lung cancer than nonsmokers who carry the same mutation,* [29] *and carriers of RB1 mutations, which are associated with retinoblastoma, also have a high lifetime risk of lung cancer …*"

Breast Cancer: " Only a small proportion (≤10%) of breast cancers are due to hereditary mutations in single, dominantly acting genes, although models suggest that a larger fraction of so-called sporadic cases of breast cancer might be attributable to the action of multiple genes.48 The two most important breast-cancer genes, *BRCA1* and *BRCA2,* confer a risk of breast cancer among carriers that is 10 to 30 times as high as the risk among women in the general population. 49 Other genes with a population frequency and risk profile similar to *BRCA1* or *BRCA2* are unlikely to exist. Less frequent mutations associated with a relative risk of breast cancer of 2.0 or greater have been identified …"

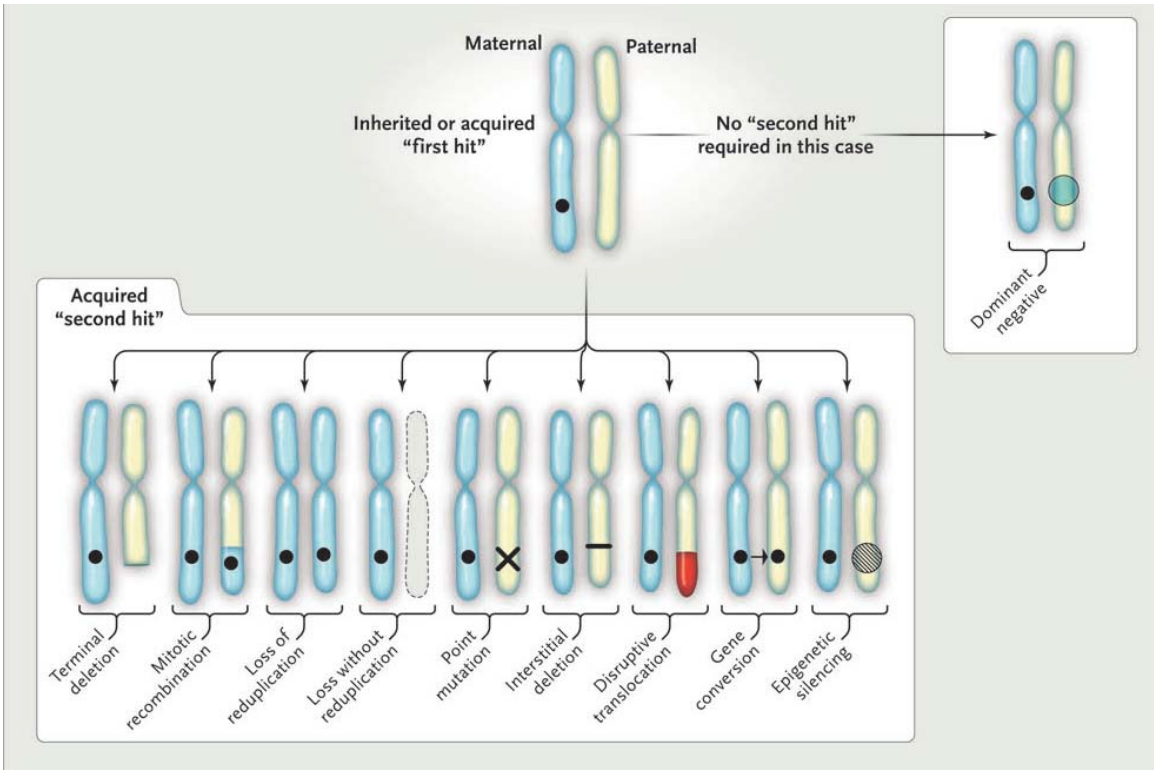
Colorectal: "There are three classes of colorectal-cancer susceptibility genes…. Several of the most important genes — *APC*, *MUTYH* (familial forms of polyposis), and the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) — account for less than 5% of

all cases of colorectal cancer, but they affect young people disproportionately (see the table in the Supplementary Appendix). Testing for mutations in these genes is recommended in patients with clinicopathological features that are suggestive of these syndromes…. The underlying defect in the Lynch syndrome is defective mismatch repair. Mismatches between DNA strands that occur naturally, but erroneously, during DNA replication are not repaired because the key genes have become inactivated, usually by two "hits" — one inherited, the other acquired later in life….. This lack of repair results in numerous DNA sequence errors, particularly in runs of tandemly repeated nucleotides such as $(T)_n$ or $(CA)_n$, where n is usually 5 or more. Errors occurring in critical genes such as *BAX* or *TGFBRII* can initiate tumors. Since this mutator phenotype accelerates the rate of carcinogenesis and results in the rapid development of colorectal cancer once polyps have formed, frequent colonoscopic screening in carriers is warranted…"

Prostate: "Unraveling the genetics of prostate cancer has been difficult, and no high-risk, prostate-specific genes seem to exist. The closest candidate is *BRCA2*, which confers a risk of prostate cancer that is as much as 20 times the risk in the general population.[84] *BRCA2*-associated prostate cancers are aggressive, suggesting the need for better screening in carriers. *BRCA2* mutations are rare; however, in men with prostate cancer, and despite considerable collaborative efforts, no prostate-cancer genes have yet been conclusively identified by linkage analysis. Genomewide association studies have identified several new candidate genes and loci. None of these genes are associated with large risks, although some are of considerable interest. The variant near the gene *MSMB* is the most promising because it encodes an immunoglobulin-binding factor that is present in seminal fluid.[19] There are several different risk loci on chromosome 8q24, and some of them are very frequent, especially in blacks, a population with a high prevalence of prostate cancer…"

2.2 GENETIC FLAWS

There are many types of genetic flaws. Faulkes also presents an interesting picture of these as shown below.



Faulkes also summarizes the major genetic defects in the following Table.

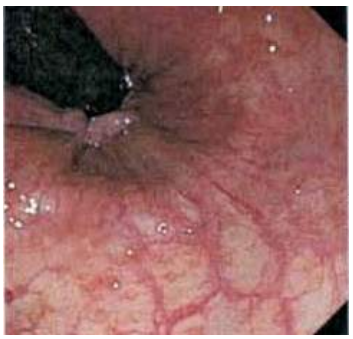
Gene	*Phenotypic Effect*
MLH1	Monoallelic Mutations Biallelic Mutations Lynch syndrome; cancers of colorectum, endo- CMMR-D syndrome (mainly in children and adolescents); metrium, small bowel, ureter, renal pelvis parents may have Lynch syndrome
MSH2	Lynch syndrome; extracolonic cancers are CMMR-D syndrome (mainly in children and adolescents); frequent parents may have Lynch syndrome
MSH6	Lynch syndrome; endometrial cancer is common, CMMR-D syndrome (mainly in children and adolescents); other cancers are less common parents may have Lynch syndrome
PMS2	Lynch syndrome; lower risk of colorectal and ex-CMMR-D syndrome (mainly in children and adolescents); tracolonic cancers cancer in previous generations uncommon
BRCA2	Hereditary breast cancer; ovarian, fallopian- tube, Fanconi's anemia, type D1; early- childhood acute myel-peritoneal, and pancreatic cancer and melanoma oid leukemia; medulloblastoma; Wilms' tumor
PALB2	Breast cancer, can be familial Fanconi's anemia, type N; early-childhood acute myelo- id leukemia; medulloblastoma; Wilms' tumor
BRIP1	Breast cancer, can be familial Fanconi's anemia, type J; solid tumors
ATM	Breast cancer, can be familial; T-cell leukemia Ataxia–telangiectasia, childhood and adolescent lymphomas and T-cell leukemia; a wide variety of carcinomas may develop late

3 TARGET DISEASE SETS

The following is a summary of the eight targeted cancers. The information is taken with modification from the National Cancer Institute web site for professionals.

3.1 COLON CANCER

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. Surgery is the primary form of treatment and results in cure in approximately 50% of the patients. Recurrence following surgery is a major problem and is often the ultimate cause of death.



Colonoscopy is the gold standard for determining whether there are polyps or other precancerous growths in the colon. The procedure, if performed by an experience endoscopist, can achieve high levels of specificity and significance. Also use of colonoscopy allow for the real time removal of most if not all lesions for subsequent biopsy.

3.1.1 Prognostic Factors

The prognosis of patients with colon cancer is clearly related to the degree of penetration of the tumor through the bowel wall, the presence or absence of nodal involvement, and the presence or absence of distant metastases. These three characteristics form the basis for all staging systems developed for this disease. Bowel obstruction and bowel perforation are indicators of poor prognosis. Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance. The American Joint Committee on Cancer and a National Cancer Institute-sponsored panel recommended that at least 12 lymph nodes be examined in patients with colon and rectal cancer to confirm the absence of nodal involvement by tumor.

This recommendation takes into consideration that the number of lymph nodes examined is a reflection of the aggressiveness of lymphovascular mesenteric dissection at the time of surgical resection and the pathologic identification of nodes in the specimen. Retrospective studies demonstrated that the number of lymph nodes examined in colon and rectal surgery may be associated with patient outcome.

Many other prognostic markers have been evaluated retrospectively for patients with colon cancer, though most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated. Microsatellite instability, also associated with hereditary nonpolyposis colon cancer (HNPCC), has been associated with improved survival independent of tumor stage in a population-based series of 607 patients younger than 50 years with colorectal cancer. Treatment decisions depend on factors such as physician and patient preferences and the stage of the disease rather than the age of the patient. Racial differences in overall survival after adjuvant therapy have been observed, without differences in disease-free survival, suggesting that comorbid conditions play a role in survival outcome in different patient populations.

3.1.2 Risk Factors

Because of the frequency of the disease, ability to identify high-risk groups, demonstrated slow growth of primary lesions, better survival of patients with early-stage lesions, and relative simplicity and accuracy of screening tests, screening for colon cancer should be a part of routine care for all adults aged 50 years or older, especially for those with first-degree relatives with colorectal cancer. Groups that have a high incidence of colorectal cancer include those with hereditary conditions, such as familial polyposis, HNPCC or Lynch syndrome variants I and II, and those with a personal history of ulcerative colitis or Crohn colitis. Together, they account for 10% to 15% of colorectal cancers. Patients with HNPCC reportedly have better prognoses in stage-stratified survival analysis than patients with sporadic colorectal cancer, but the retrospective nature of the studies and possibility of selection factors make this observation difficult to interpret.

More common conditions with an increased risk include a personal history of colorectal cancer or adenomas; first-degree family history of colorectal cancer or adenomas; and a personal history of ovarian, endometrial, or breast cancer. These high-risk groups account for only 23% of all colorectal cancers. Limiting screening or early cancer detection to only these high-risk groups would miss the majority of colorectal cancers.

3.1.3 Follow-up

Following treatment of colon cancer, periodic evaluations may lead to the earlier identification and management of recurrent disease. The impact of such monitoring on overall mortality of patients with recurrent colon cancer, however, is limited by the relatively small proportion of patients in who localized, potentially curable metastases are found. To date, no large-scale randomized trials have documented the efficacy of a standard, postoperative monitoring program. CEA is a serum glycoprotein frequently used in the management of patients with colon cancer. A review of the use of this tumor marker suggests the following:

A CEA level is not a valuable screening test for colorectal cancer because of the large numbers of false-positive and false-negative reports.

Postoperative CEA testing should be restricted to patients who would be candidates for resection of liver or lung metastases.
Routine use of CEA levels alone for monitoring response to treatment should not be recommended.

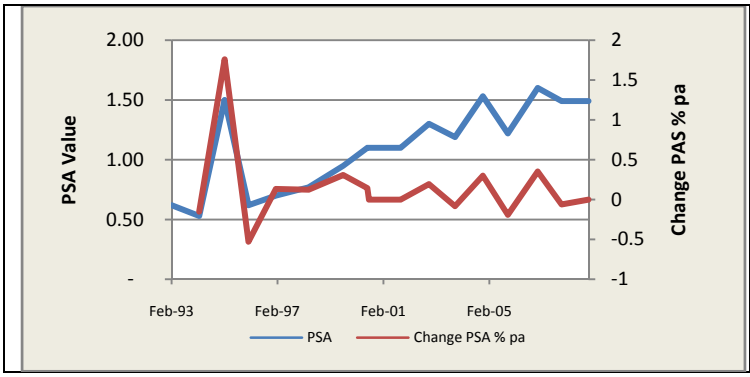
The optimal regimen and frequency of follow-up examinations are not well defined because the impact on patient survival is not clear, and the quality of data is poor. New surveillance methods, including CEA immunoscintigraphy and positron emission tomography, are under clinical evaluation.

3.1.4 Statistics

Estimated new cases and deaths from colon cancer in the United States in 2008: 1
New cases: 108,070.
Deaths (colon and rectal cancers combined): 49,960.

3.2 PROSTATE CANCER

Carcinoma of the prostate is predominantly a tumor of older men, which frequently responds to treatment when widespread and may be cured when localized. The rate of tumor growth varies from very slow to moderately rapid, and some patients may have prolonged survival even after the cancer has metastasized to distant sites such as bone. Because the median age at diagnosis is 72 years, many patients—especially those with localized tumors—may die of other illnesses without ever having suffered significant disability from the cancer. The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management. Controversy exists in regard to the value of screening, the most appropriate staging evaluation, and the optimal treatment of each stage of the disease.



PSA Values are a way to monitor possible progression to prostate cancer. It is the absolute value, less than 4 and the rate of change, less than 25% per annum.

A complicating feature of any analysis of survival after treatment of prostate cancer and comparison of the various treatment strategies is the evidence of increasing diagnosis of nonlethal tumors as diagnostic methods have changed over time. Nonrandomized comparisons of treatments may therefore be confounded not only by patient-selection factors but also by time trends. For example, a population-based study in Sweden showed that from 1960 to the late 1980s, before the use of prostate-specific antigen (PSA) for screening purposes, long-term relative survival rates after the diagnosis of prostate cancer improved substantially as more sensitive methods of diagnosis were introduced. This occurred despite the use of watchful waiting or palliative hormonal treatment as the most common treatment strategies for localized prostate cancer during the entire era (<150 radical prostatectomies per year were performed in Sweden during the late 1980s). The investigators estimated that if all cancers diagnosed between 1960 and 1964 were of the lethal variety, then at least 33% of cancers diagnosed between 1980 and 1984 were of the nonlethal variety. With the advent of PSA screening, the ability to diagnose nonlethal prostate cancers may increase further.

Another issue complicating comparisons of outcomes among nonconcurrent series of patients is the possibility of changes in criteria for histologic diagnosis of prostate cancer. This phenomenon creates a statistical artifact that can produce a false sense of therapeutic accomplishment and may also lead to more aggressive therapy. For example, prostate biopsies from a population-based cohort of 1,858 men diagnosed with prostate cancer from 1990 through 1992 were re-read in 2002 to 2004. The contemporary Gleason score readings were an average of 0.85 points higher (95% confidence interval, 0.79–0.91; $P < .001$) than the same slides read in 1990 to 1992. As a result, Gleason score-standardized prostate cancer mortality for these men was artifactually improved from 2.08 to 1.50 deaths per 100 person years—a 28% decrease even though overall outcomes were unchanged.

3.2.1 Screening

The issue of screening asymptomatic men for prostate cancer with digital rectal examination (DRE), PSA, and/or ultrasound is controversial. Serum PSA and transrectal ultrasound are more sensitive and will increase the diagnostic yield of prostate cancer when used in combination with rectal examination; however, these screening methods are also associated with high false-positive rates and may identify some tumors that will not threaten the patient's health. The issue is further complicated by the morbidity associated with work-up and treatment of such tumors and the considerable cost beyond a routine DRE. Furthermore, because a high percentage of tumors identified by PSA screening alone have spread outside the prostate, PSA screening may not improve life expectancy. In any case, the clinician who uses PSA for the detection of prostate cancer should be aware that no uniform standard exists; if a laboratory changes to a different assay kit, serial assays may yield nonequivalent PSA values. In addition, the upper limit of the normal range of PSA, and therefore the threshold at which to biopsy,

is not well-defined. A multicenter trial (PLCO-1) sponsored by the National Cancer Institute is under way to test the value of early detection in reducing mortality.

Survival of the patient with prostatic carcinoma is related to the extent of the tumor. When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. Patients with locally advanced cancer are not usually curable, and a substantial fraction will eventually die of the tumor, though median survival may be as long as 5 years. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most such patients will die of prostate cancer. Even in this group of patients, however, indolent clinical courses lasting for many years may be observed.

3.2.2 PSA Prognosis

Other factors affecting the prognosis of patients with prostate cancer that may be useful in making therapeutic decisions include histologic grade of the tumor, patient's age, other medical illnesses, and level of PSA. Poorly differentiated tumors are more likely to have already metastasized by the time of diagnosis and are associated with a poorer prognosis. For patients treated with radiation therapy, the combination of clinical tumor stage, Gleason score, and pretreatment PSA level can be used to more accurately estimate the risk of relapse. In most studies, flow cytometry has shown that nuclear DNA ploidy is an independent prognostic indicator for progression and for cause-specific survival in patients with pathologic stages III and IV prostate cancer without metastases (Jewett stages C and D1). Diploid tumors have a more favorable outcome than either tetraploid or aneuploid tumors. The use of flow cytometry techniques and histogram analysis to determine prognosis will require standardization.

Often, baseline rates of PSA changes are thought to be markers of tumor progression. Even though a tumor marker or characteristic may be consistently associated with a high risk of prostate cancer progression or death, it may be a very poor predictor and therefore of very limited utility in making therapeutic decisions. For example, baseline PSA and rate of PSA change were associated with subsequent metastasis or prostate cancer death in a cohort of 267 men with clinically localized prostate cancer who were managed by watchful waiting in the control arm of a randomized trial comparing radical prostatectomy to watchful waiting. Nevertheless, the accuracy of classifying men into groups whose cancer remained indolent versus those whose cancer progressed was poor at all examined cut points of PSA or PSA rate of change.

Several nomograms have been developed to predict outcomes either prior to or after radical prostatectomy with intent to cure. Preoperative nomograms are based on clinical stage, PSA, Gleason score, and the number of positive and negative prostate biopsy cores. Postoperative nomograms add pathologic findings, such as capsular invasion, surgical margins, seminal vesicle invasion, and lymph node involvement. The nomograms, however, were developed at academic centers and may not be as accurate

when generalized to nonacademic hospitals, where the majority of patients are treated. In addition, the nomograms use nonhealth (intermediate) outcomes such as PSA rise or pathologic surgical findings and subjective endpoints such as the physician's perceived need for additional therapy. In addition, the nomograms may be affected by changing methods of diagnosis or neoadjuvant therapy.

Definitive treatment is usually considered for younger men with prostate cancer and no major comorbid medical illnesses because younger men are more likely to die of prostate cancer than older men or men with major comorbid medical illness. Elevations of serum acid phosphatase are associated with poor prognosis in both localized and disseminated disease. PSA, an organ-specific marker with greater sensitivity and high specificity for prostate tissue, is often used as a tumor marker. After radical prostatectomy, detectable PSA levels identify patients at elevated risk of local treatment failure or metastatic disease; however, a substantial proportion of patients with elevated or rising PSA levels after surgery may remain clinically free of symptoms for extended periods of time.

Biochemical evidence of failure on the basis of elevated or slowly rising PSA alone therefore may not be sufficient to alter treatment. For example, in a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years, 315 men (15%) demonstrated an abnormal PSA of 0.2 ng/mL or higher, which is evidence of biochemical recurrence. Of these 315 men, 103 men (34%) developed clinical evidence of recurrence. The median time to development of clinical metastasis after biochemical recurrence was 8 years. After the men developed metastatic disease, the median time to death was an additional 5 years.

After radiation therapy with curative intent, persistently elevated or rising PSA may be a prognostic factor for clinical disease recurrence; however, reported case series have used a variety of definitions of PSA failure. Criteria have been developed by the American Society for Therapeutic Radiology and Oncology Consensus Panel. It is difficult to base decisions about instituting additional therapy on biochemical failure. The implication of the various definitions of PSA failure for overall survival (OS) is not known, and as in the surgical series, many biochemical relapses (rising PSA alone) may not be clinically manifested in patients treated with radiation therapy.

Using surrogate endpoints for clinical decision making is controversial. Preliminary data from a retrospective cohort of 8,669 patients with clinically localized prostate cancer treated with either radical prostatectomy or radiation therapy suggested that short post treatment PSA doubling time (<3 months in this study) fulfills some criteria as a surrogate endpoint for all-cause mortality and prostate cancer mortality after surgery or radiation therapy. Likewise, a retrospective analysis has shown that PSA declines of 20% to 40% (but not 50%) at 3 months and 30% or more at 2 months after initiation of chemotherapy for hormone independent prostate cancer, fulfilled several criteria of

surrogacy for OS. These observations should be independently confirmed in prospective study designs and may not apply to patients treated with hormonal therapy. In addition, there are no standardized criteria of surrogacy or standardized cutpoints for adequacy of surrogate endpoints, even in prospective trials.

After hormonal therapy, reduction of PSA to undetectable levels provides information regarding the duration of progression-free status; however, decreases in PSA of less than 80% may not be very predictive. Yet, because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum level of PSA independent of tumor response. Clinicians, therefore, cannot rely solely on the serum PSA level to monitor a patient's response to hormone therapy; they must also follow clinical criteria.

3.2.3 Statistics

Estimated new cases and deaths from prostate cancer in the United States in 2008:
New cases: 186,320.
Deaths: 28,660.

3.2.4 Recent Studies

The New England Journal of Medicine published two studies recently 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, one Gina Kolata, states:

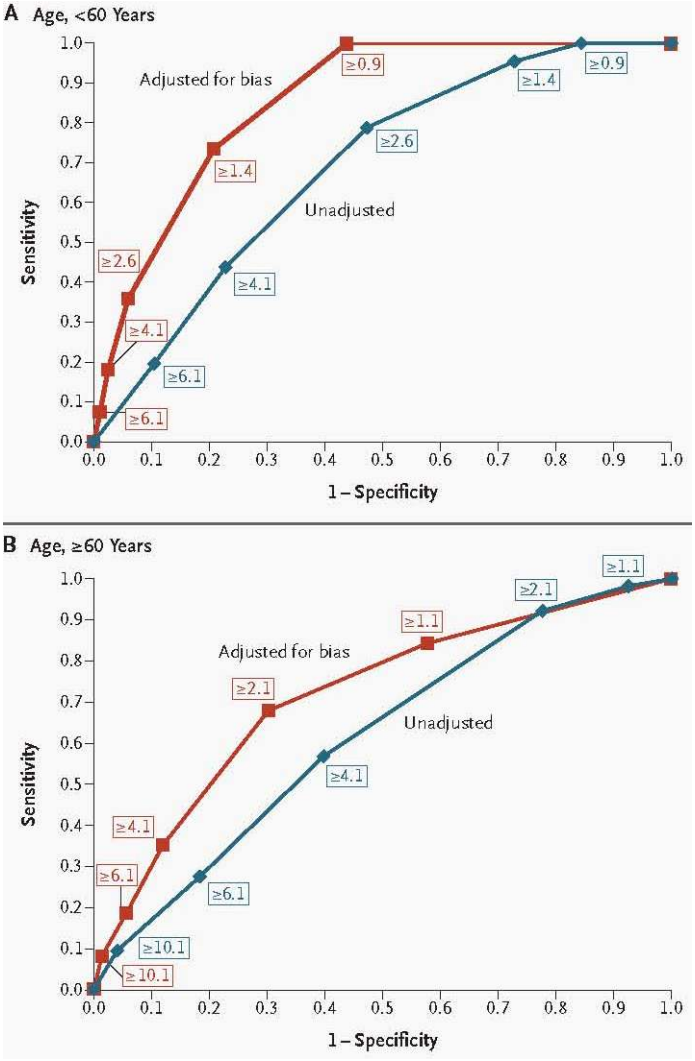
"The PSA test, which measures a protein released by prostate cells, does what it is supposed to do — indicates a cancer might be present, leading to biopsies to determine if there is a tumor. But it has been difficult to know whether finding prostate cancer early saves lives. Most of the cancers tend 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.

However the question that should have been posed in the testing is:

"What PSA level should lead to further testing such that there is a material reduction in mortality from Prostate Cancer?"

A corollary question would also be posed:

"What level of PSA and what velocity of PSA should lead to further evaluation and remediation so as to materially reduce prostate cancer mortality and/or significantly reduce the burden on the health care system subject to a constraint on a quality of life standard?"

Apparently all of this work assumed a PSA limit of 4.0 to be a golden standard. That seems not to be the case. However, as interpreted, this appears to have been common knowledge as far back as 2003 but was neglected to be included in the study albeit referred to in the American study.

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 apposition 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. "

The following Table is from Tomlin:

Table 1. Cancer outlier profile analysis (COPA). Genes known to undergo causal mutations in cancer that had strong outlier profiles. ‘‘X’’ indicates literature evidence for the acquired pathognomonic translocation. ‘‘XX’’ indicate that samples in the study were characterized for the indicated translocation. ‘‘Y’’ indicates consistent with known amplification. Double asterisks indicate ERG and ETV1 outlier profiles in prostate cancer. A complete listing of genes known to undergo causal mutations ranking in the top 10 of all studies in Oncomine, along with the relevant references, is included as table S1.

Rank	%	Score	Gene	Cancer	Study	Evidence
1	95	20.06	RUNX1T1	Leukemia	(23)	XX
1	95	15.45	PRO1073	Renal	(24)	X
1	90	12.96	PBX1	Leukemia	(25)	XX
1	95	10.04	ETV1	Prostate	(15)	**
1	90	7.46	WHSC1	Myeloma	(26)	X
1	75	5.41	ERG	Prostate	(27)	**
1	75	4.36	ERG	Prostate	(28)	**
1	75	4.34	CCND1	Myeloma	(29)	X
1	75	3.44	ERG	Prostate	(15)	**
1	75	3.39	ERG	Prostate	(30)	**
3	95	13.35	FGFR3	Myeloma	(29)	X
4	75	2.57	ERBB2	Breast	(31)	Y
6	90	6.61	ERBB2	Breast	(32)	Y
9	95	17.17	ETV1	Prostate	(16)	**
9	90	6.61	SSX1	Sarcoma	(33)	X
9	75	2.22	ERG	Prostate	(34)	**

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.

3.3 BREAST CANCER

Breast cancer is a highly aggressive cancer which can be managed and potentially cured if detected early. Breast cancer also has a strong genetic relationship in several cases.

3.3.1 Genetic Characteristics and Risk Factors

Several well-established factors have been associated with an increased risk of breast cancer, including family history, nulliparity, early menarche, advanced age, and a personal history of breast cancer (*in situ* or invasive).

Age-specific risk estimates are available to help counsel and design screening strategies for women with a family history of breast cancer. Of all women with breast cancer, 5% to 10% may have a germ-line mutation of the genes *BRCA1* and *BRCA2*. Specific mutations of *BRCA1* and *BRCA2* are more common in women of Jewish ancestry. The estimated lifetime risk of developing breast cancer for women with *BRCA1* and *BRCA2* mutations is 40% to 85%. Carriers with a history of breast cancer have an increased risk of contralateral disease that may be as great as 5% per year. Male carriers of *BRCA2* mutations are also at increased risk for breast cancer.

Mutations in either the *BRCA1* or *BRCA2* gene also confer an increased risk of ovarian cancer. In addition, mutation carriers may be at increased risk of other primary cancers. Genetic testing is available to detect mutations in members of high-risk families. Such individuals should first be referred for counseling.

3.3.2 Screening

Clinical trials have established that screening with mammography, with or without clinical breast examination, may decrease breast cancer mortality.

3.3.3 Patient Evaluation

Patient management following initial suspicion of breast cancer generally includes confirmation of the diagnosis, evaluation of stage of disease, and selection of therapy. At the time the tumor tissue is surgically removed, estrogen receptor (ER) and progesterone receptor (PR) status should be determined.

3.3.4 Prognostic Factors

Breast cancer is commonly treated by various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. Prognosis and selection of therapy may be influenced by:

- The age and menopausal status of the patient.
- The stage of the disease.
- The histologic and nuclear grade of the primary tumor.
- The ER and PR status of the tumor.
- The measures of proliferative capacity of the tumor.
- HER2/neu gene amplification.

Although certain rare inherited mutations such as those of *BRCA1* and *BRCA2* predispose women to develop breast cancer, prognostic data on mutation carriers who have developed breast cancer are conflicting. Since criteria for menopausal status vary widely, some studies have substituted age older than 50 years as a surrogate for the postmenopausal state. Breast cancer is classified into a variety of histologic types, some of which have prognostic importance. For example, favorable histologic types include mucinous, medullary, and tubular carcinoma.

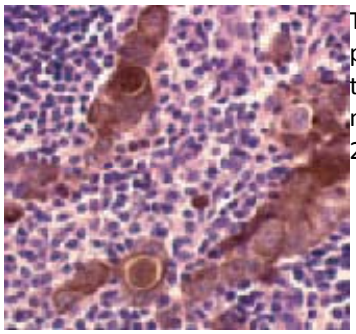
3.3.5 Statistics

Estimated new cases and deaths from breast cancer (women only) in the United States in 2008:

New cases: 182,460.
Deaths: 40,480.

3.4 MELANOMA

Melanoma is a malignant tumor of melanocytes, which are the cells that make the pigment melanin and are derived from the neural crest. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than 50% of the cases arise in apparently normal areas of the skin. Early signs in a nevus that would suggest malignant change include darker or variable discoloration, itching, an increase in size, or the development of satellites. Ulceration or bleeding is later signs. Melanoma in women occurs more commonly on the extremities and in men on the trunk or head and neck, but it can arise from any site on the skin surface.



The pathology slide on the left depicts a malignant melanoma. The cells proliferate from a clonal melanocytes in the basal layer of the skin and then enter the blood stream for rapid hematological spread. There are metastases to the brain and elsewhere. From Miller, Melanoma, NEJM, 2006; 355:51-65.

3.4.1 Diagnosis

A biopsy, preferably by local excision, should be performed for any suspicious lesions, and the specimens should be examined by an experienced pathologist to allow for microstaging. Suspicious lesions should never be shaved off or cauterized. Studies show that distinguishing between benign pigmented lesions and early melanomas can be

difficult, and even experienced dermatopathologists can have differing opinions. To reduce the possibility of misdiagnosis for an individual patient, a second review by an independent qualified pathologist should be considered.

Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, presence of tumor infiltrating lymphocytes, number of regional lymph nodes involved, and ulceration or bleeding at the primary site affect the prognosis. Microscopic satellites in stage I melanoma may be a poor prognostic histologic factor, but this is controversial. Patients who are younger, female, and who have melanomas on the extremities generally have a better prognosis.

3.4.2 Genetic Analysis of Melanoma

A great deal of research has been done on the genetic fabric of melanoma. There is no simple answer as to the genetic initiation but the recent work by Curtin et al details the many genetic underpinnings of the malignancy. Specifically Curtin et al concluded in their recent paper:

"Knowledge of the genetic differences among melanomas could be valuable in the design of therapeutic strategies. Our results lead us to make a prediction. The group of tumors on skin without chronic sun-induced damage, which represent the most common type of melanoma, frequently had a mutation in BRAF together with a loss of PTEN or mutations in N-RAS alone. Thus, they would be expected to be responsive to therapeutic interventions targeting the RAS–RAF–ERK and PI3K pathways. In contrast, the majority of melanomas in the other three groups did not have mutations in BRAF or N-RAS but instead had increased numbers of copies of the downstream gene CCND1 or CDK4.

Thus, these three groups of melanomas would be less likely to respond to therapeutic interventions that target upstream components of the mitogen-activated protein kinase pathway including BRAF, such as sorafenib. Our study provides genetic support for the existence of distinct molecular pathways to melanoma, each with a unique relationship to exposure to ultraviolet light. This finding should affect the design of future studies involving the treatment and prevention of melanoma and suggests the existence of as yet- unidentified susceptibility factors."

The results of Curtin seem to imply that the sun damaged generation of melanoma may be more difficult to treat than the non-sun damaged variety, specifically due to the origin from differing genetic pathways. Second, the approach taken by Curtin et al may raise the question as to the MPM syndrome.

As to the MPM and genetic markers relationship, Ferrone has stated:

"Several risk factors associated with the development of MPM have been identified. These include a positive family history of MPM and a personal history of dysplastic nevi (DN); atypical moles that are risk markers but non-obligate precursors of melanoma. Among patients with MPM, 18% to 38% are reported to have a positive family history of melanoma and 38% to 46% are reported to have a history of dysplastic nevi. However, few longitudinal cohort-defined databases have prospectively recorded known risk factors for all patients with melanoma to assess the impact of these risk factors on the development of MPM."

Thus, as to our Case patient, we were not able to determine a full family history and thus this leaves the consideration of this being an MPM syndrome open to question. Specifically family history as well as dysplastic nevus syndrome, clearly ascertained by pathological analysis, is an essential in a proper diagnosis as well as treatment.

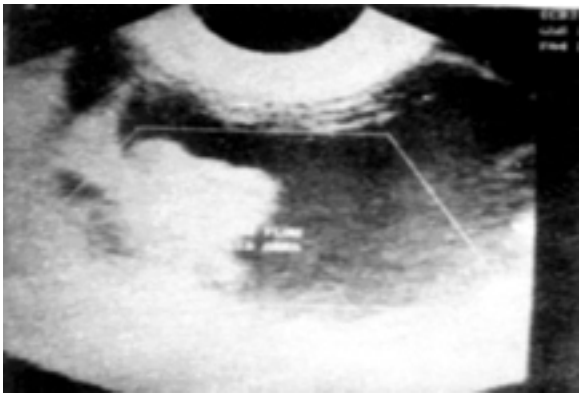
3.4.3 Statistics

Estimated new cases and deaths from melanoma in the United States in 2008:

New cases: 62,480.
Deaths: 8,420.

3.5 OVARIAN CANCER

Several malignancies arise from the ovary. Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women older than 65 years. Approximately 5% to 10% of ovarian cancers are familial and three distinct hereditary patterns have been identified: ovarian cancer alone, ovarian and breast cancers, or ovarian and colon cancers. The most important risk factor for ovarian cancer is a family history of a first-degree relative (e.g., mother, daughter, or sister) with the disease. The highest risk appears in women with two or more first-degree relatives with ovarian cancer. The risk is somewhat less for women with one first-degree and one second-degree relative (grandmother or aunt) with ovarian cancer.



Transvaginal ultrasound is the initial gold standard for the detection of o0varian lesions. The ultrasound lesion shown to the left shows an ovary with a solid mass interior and is most likely a carcinoma.

3.5.1 Genetics

In most families affected with the breast and ovarian cancer syndrome or site-specific ovarian cancer, genetic linkage has been found to the BRCA1 locus on chromosome 17q21. BRCA2, also responsible for some instances of inherited ovarian and breast cancer, has been mapped by genetic linkage to chromosome 13q12. The lifetime risk for developing ovarian cancer in patients harboring germline mutations in BRCA1 is substantially increased over the general population. Two retrospective studies of patients with germline mutations in BRCA1 suggest that these women have improved survival compared with BRCA1-mutation–negative women. The majority of women with a BRCA1 mutation probably have family members with a history of ovarian and/or breast cancer; therefore, these women may have been more vigilant and inclined to participate in cancer screening programs that may have led to earlier detection.

3.5.2 Treatment

For women at increased risk, prophylactic oophorectomy may be considered after the age of 35 if childbearing is complete. In a family-based study among women with BRCA1 or BRCA2 mutations, of the 259 women who had undergone bilateral prophylactic oophorectomy, two of them (0.8%) developed subsequent papillary serous peritoneal carcinoma, and six of them (2.8%) had stage I ovarian cancer at the time of surgery. Of the 292 matched controls, 20% who did not have prophylactic surgery developed ovarian cancer. Prophylactic surgery was associated with a higher than 90% reduction in the risk of ovarian cancer (relative risk = 0.04; 95% confidence interval , 0.01–0.16), with an average follow-up of 9 years; however, family-based studies may be associated with biases resulting from case selection and other factors that may influence the estimate of benefit.

After a prophylactic oophorectomy, a small percentage of women may develop a primary peritoneal carcinoma, similar in appearance to ovarian cancer. The prognostic information presented below deals only with epithelial carcinomas. Stromal and germ cell tumors are relatively uncommon and comprise less than 10% of cases.

Ovarian cancer usually spreads via local shedding into the peritoneal cavity followed by implantation on the peritoneum and via local invasion of bowel and bladder. The incidence of positive nodes at primary surgery has been reported to be as much as 24% in patients with stage I disease, 50% in patients with stage II disease, 74% in patients with stage III disease, and 73% in patients with stage IV disease. In this study, the pelvic nodes were involved as often as the para-aortic nodes. Tumor cells may also block diaphragmatic lymphatics. The resulting impairment of lymphatic drainage of the peritoneum is thought to play a role in development of ascites in ovarian cancer. Also, transdiaphragmatic spread to the pleura is common.

3.5.3 Prognosis

Prognosis in ovarian cancer is influenced by several factors, but multivariate analyses suggest that the most important favorable factors include:

- Younger age.
- Good performance status.
- Cell type other than mucinous and clear cell.
- Lower stage.
- Well-differentiated tumor.
- Smaller disease volume prior to any surgical debulking.
- Absence of ascites.
- Smaller residual tumor following primary cytoreductive surgery.

For patients with stage I disease, the most important prognostic factor is grade, followed by dense adherence and large-volume ascites. DNA flow cytometric analysis of stage I and stage IIA patients may identify a group of high-risk patients. Patients with clear cell histology appear to have a worse prognosis. Patients with a significant component of transitional cell carcinoma appear to have a better prognosis.

3.5.4 Detection

Although the ovarian cancer-associated antigen, CA 125, has no prognostic significance when measured at the time of diagnosis, it has a high correlation with survival when measured 1 month after the third course of chemotherapy for patients with stage III or stage IV disease. For patients whose elevated CA 125 normalizes with chemotherapy, more than one subsequent elevated CA 125 measurement is highly predictive of active disease, but this does not mandate immediate therapy.

Most patients with ovarian cancer have widespread disease at presentation. This may be partly explained by relatively early spread (and implantation) of high grade papillary serous cancers to the rest of the peritoneal cavity. Conversely, symptoms such as

abdominal pain and swelling, gastrointestinal symptoms, and pelvic pain, often go unrecognized, leading to delays in diagnosis. As a result of these confounding factors, yearly mortality in ovarian cancer is approximately 65% of the incidence rate. Long-term follow-up of suboptimally debulked stage III and stage IV patients showed a 5-year survival rate of less than 10% with platinum-based combination therapy prior to the current generation of trials including taxanes.

By contrast, optimally debulked stage III patients treated with a combination of intravenous taxane and intraperitoneal platinum plus taxane achieved a median survival of 66 months in a Gynecologic Oncology Group trial. Numerous clinical trials are in progress to refine existing therapy and test the value of different approaches to postoperative drug and radiation therapy.

3.5.5 Statistics

Estimated new cases and deaths from ovarian cancer in the United States in 2008:

New cases: 21,650.
Deaths: 15,520.

3.6 LUNG CANCER

Small cell lung cancer (SCLC) accounts for approximately 15% of bronchogenic carcinomas. The overall incidence and mortality rates of SCLC in the United States have decreased during the past few decades. Without treatment, SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 to 4 months. Compared with other cell types of lung cancer, SCLC is more responsive to chemotherapy and radiation therapy; however, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis. It is the cancer most commonly associated with paraneoplastic syndromes, including the syndrome of inappropriate antidiuretic hormone secretion, paraneoplastic cerebellar degeneration, and Lambert-Eaton myasthenic syndrome.

3.6.1 Limited-Stage Disease

At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited-stage disease (LD), and most 2-year disease-free survivors come from this group. For patients with LD, median survival of 16 to 24 months and 5-year survivals of 14% with current forms of treatment have been reported. Patients diagnosed with LD who smoke should be encouraged to stop smoking before undergoing combined-modality therapy because continued smoking may compromise cure rates.

Improved long-term survival has been shown with combined modality therapy. Although long-term survivors have been reported among patients who received either surgery or chemotherapy alone, chemotherapy combined with thoracic radiation therapy (TRT) is considered the standard of care. Adding TRT increases absolute survival by approximately 5% over chemotherapy alone. The optimal timing of TRT relative to chemotherapy has been evaluated in multiple trials and meta-analyses with the weight of evidence suggesting a small benefit to early TRT. Prophylactic cranial radiation prevents central nervous system (CNS) recurrence and can improve survival in patients who have had a complete response to chemoradiation.

3.6.2 Extensive-Stage Disease

Patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease (ED) and have a worse prognosis than patients with LD. Median survival of 6 to 12 months is reported with currently available therapy, but long-term disease-free survival is rare.

3.6.3 Prognostic Factors

The pretreatment prognostic factors that consistently predict for prolonged survival include good performance status, female gender, and LD. Patients with involvement of the CNS or liver at the time of diagnosis have a significantly worse outcome. A number of biochemical factors including serum sodium, alkaline phosphatase, and lactate dehydrogenase have also been found to independently correlate with outcome.
Regardless of stage, the current prognosis for patients with SCLC is unsatisfactory despite improvements in diagnosis and therapy made during the past 25 years. All patients with this type of cancer may appropriately be considered for inclusion in clinical trials at the time of diagnosis.

3.6.4 Statistics

Estimated new cases and deaths from lung cancer (small cell lung cancer and non-small cell lung cancer combined) in the United States in 2008:

New cases: 215,020.
Deaths: 161,840.

3.7 CERVIX

The prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. Because a vast majority (>90%) of these cases can and should be detected early through the use of the Pap smear, the current death rate is far

higher than it should be and reflects that, even today, Pap smears are not done on approximately 33% of eligible women.

3.7.1 Prognosis

Among the major factors that influence prognosis are stage, volume and grade of tumor, histologic type, lymphatic spread, and vascular invasion. In a large surgicopathologic staging study of patients with clinical stage IB disease reported by the Gynecologic Oncology Group (GOG), the factors that predicted most prominently for lymph node metastases and a decrease in disease-free survival were capillary-lymphatic space involvement by tumor, increasing tumor size, and increasing depth of stromal invasion, with the latter being most important and reproducible. In a study of 1,028 patients treated with radical surgery, survival rates correlated more consistently with tumor volume (as determined by precise volumetry of the tumor) than clinical or histologic stage.

A multivariate analysis of prognostic variables in 626 patients with locally advanced disease (primarily stages II, III, and IV) studied by the GOG revealed that periaortic and pelvic lymph node status, tumor size, patient age, and performance status were significant for progression-free interval and survival. The study confirms the overriding importance of positive periaortic nodes and suggests further evaluation of these nodes in locally advanced cervical cancer. The status of the pelvic nodes was important only if the periaortic nodes were negative. This was also true for tumor size.

Bilateral disease and clinical stage were also significant for survival. In a large series of cervical cancer patients treated by radiation therapy, the incidence of distant metastases (most frequently to lung, abdominal cavity, liver, and gastrointestinal tract) was shown to increase as the stage of disease increased, from 3% in stage IA to 75% in stage IVA. A multivariate analysis of factors influencing the incidence of distant metastases showed stage, endometrial extension of tumor, and pelvic tumor control to be significant indicators of distant dissemination.

Whether adenocarcinoma of the cervix carries a significantly worse prognosis than squamous cell carcinoma of the cervix remains controversial. Reports conflict about the effect of adenosquamous cell type on outcome. One report showed that approximately 25% of apparent squamous tumors have demonstrable mucin production and behave more aggressively than their pure squamous counterparts, suggesting that any adenomatous differentiation may confer a negative prognosis. The decreased survival is mainly the result of more advanced stage and nodal involvement rather than cell type as an independent variable. Women with human immunodeficiency virus have more aggressive and advanced disease and a poorer prognosis. A study of patients with known invasive squamous carcinoma of the cervix found that overexpression of the C-myc oncogene was associated with a poorer prognosis. The number of cells in S phase may also have prognostic significance in early cervical carcinoma.

3.7.2 Human papillomavirus infection and cervical cancer

Molecular techniques for the identification of human papillomavirus (HPV) DNA are highly sensitive and specific. More than 6 million women in the United States are estimated to have HPV infection, and proper interpretation of these data is important. Epidemiologic studies convincingly demonstrate that the major risk factor for development of preinvasive or invasive carcinoma of the cervix is HPV infection, which far outweighs other known risk factors such as high parity, increasing number of sexual partners, young age at first intercourse, low socioeconomic status, and positive smoking history. Some patients with HPV infection appear to be at minimal increased risk for development of cervical preinvasive and invasive malignancies, while others appear to be at significant risk and are candidates for intensive screening programs and/or early intervention.

HPV DNA tests are unlikely to separate patients with low-grade squamous intraepithelial lesions into those who do and those who do not need further evaluation. A study of 642 women found that 83% had one or more tumorigenic HPV types when cervical cytologic specimens were assayed by a sensitive (hybrid capture) technique. The authors of the study and of an accompanying editorial concluded that using HPV DNA testing in this setting does not add sufficient information to justify its cost. Whether HPV DNA testing will prove useful in patients with atypical squamous cells of undetermined significance is being studied by the same group. Patients with an abnormal cytology of a high-risk type (Bethesda classification) should be thoroughly evaluated with colposcopy and biopsy.

Other studies show patients with low-risk cytology and high-risk HPV infection with types 16, 18, and 31 are more likely to have cervical intraepithelial neoplasia (CIN) or microinvasive histopathology on biopsy. One method has also shown that integration of HPV types 16 and 18 into the genome, leading to transcription of viral and cellular messages, may predict patients who are at greater risk for high-grade dysplasia and invasive cancer. Studies suggest that acute infection with HPV types 16 and 18 conferred an 11- to 16.9-fold risk of rapid development of high-grade CIN, but there are conflicting data requiring further evaluation before any recommendations may be made.

Patients with low-risk cytology and low-risk HPV types have not been followed long enough to ascertain their risk. At present, studies are ongoing to determine how HPV typing can be used to help stratify women into follow-up and treatment groups. HPV typing may prove useful, particularly in patients with low-grade cytology or cytology of unclear abnormality. At present, how therapy and follow-up should be altered with low- versus high-risk HPV type has not been established.

3.7.3 Statistics

Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2008:

New cases: 11,070.
Deaths: 3,870.

3.8 TESTIS

Testicular cancer is a highly treatable, often curable, cancer that usually develops in young and middle-aged men. Testicular cancer is broadly divided into seminoma and nonseminoma types for treatment planning because seminomas are more sensitive to radiation therapy. For patients with seminoma (all stages combined), the cure rate exceeds 90%. For patients with low-stage disease, the cure rate approaches 100%.
Tumors that have a mixture of seminoma and nonseminoma components should be managed as nonseminomas. Nonseminomas include embryonal carcinomas, teratomas, yolk sac carcinomas, choriocarcinomas, and various combinations of these cell types. Tumors that appear to have a seminoma histology but that have elevated serum levels of alpha-fetoprotein (AFP) should be treated as nonseminomas. Elevation of the beta subunit of human chorionic gonadotropin (hCG) alone is found in approximately 10% of the patients with pure seminoma.

Risk of metastases is lowest for teratoma and highest for choriocarcinoma, with the other cell types having intermediate risk.

3.8.1 Prognosis

A number of prognostic classification schema are in use for metastatic nonseminomatous testicular cancer and for primary extragonadal nonseminomatous germ cell cancers treated with chemotherapy. Most incorporate some or all of the following factors, which may independently predict worse prognosis:

- Presence of liver, bone, or brain metastases.
- Very high serum markers.
- Primary mediastinal nonseminoma.
- Large number of lung metastases.

Even patients with widespread metastases at presentation, including those with brain metastases, may be curable and should be treated with this intent.

3.8.2 Treatment

Radical inguinal orchiectomy with initial high ligation of the spermatic cord is the procedure of choice in treating a malignant testicular mass. Transscrotal biopsy is not considered appropriate because of the risk of local dissemination of tumor into the scrotum or its spread to inguinal lymph nodes. A retrospective analysis of reported series in which transscrotal approaches had been used showed a small but statistically significant increase in local recurrence rates compared with the recurrence rates when the inguinal approach was used (2.9% vs. 0.4%). Distant recurrence and survival rates, however, were indistinguishable in the two approaches. Local recurrence was similar in patients who did not have scrotal violation, regardless of whether or not additional treatments, such as hemiscrotal radiation therapy, hemiscrotal resection, or inguinal lymph node dissection, were used.

An important aspect of the diagnosis and follow-up of testicular cancer is the use of serum markers. Serum markers include AFP, hCG (measurement of the beta subunit reduces luteinizing hormone cross-reactivity), and lactate dehydrogenase. The serum markers may detect a tumor that is too small to be discovered on physical examination or x-rays. In patients younger than 15 years, approximately 90% of testicular germ cell cancers are yolk sac tumors. In these types of patients, the AFP is elevated at diagnosis and is an excellent indicator of response to therapy and disease status. Serum markers plus chest x-rays are important parts of the monthly checkups for patients after definitive therapy of testicular cancer as well as periodic abdominal computed tomographic (CT) scans for 2 to 3 years. The absence of markers does not mean the absence of tumor. After diagnosis and treatment, patients typically receive follow-up monthly for the first year and every other month for the second year. While the majority of tumor recurrences appear within 2 years, late relapse has been reported, and lifelong marker, radiologic, and physical examination is recommended.

Evaluation of the retroperitoneal lymph nodes, usually by CT scanning, is an important aspect of treatment planning in adults with testicular cancer. Patients with a negative result however, have a 25% to 30% chance of having microscopic involvement of the lymph nodes. For seminoma, some physicians think that knowing the results of both the lymphangiogram and the CT scan is important for treatment planning. For nonseminoma, the inaccuracy of both is a problem, and frequently surgical staging is required. About 25% of patients with clinical stage I nonseminomatous testicular cancer will be upstaged to pathologic stage II with retroperitoneal lymph node dissection (RPLND), and about 25% of clinical stage II patients will be downstaged to pathologic stage I with RPLND. In children, the use of serial measurements of AFP has proven sufficient for monitoring response after initial orchiectomy. Lymphangiography and para-aortic lymph node dissection do not appear to be useful or necessary in the proper staging and management of these patients.

3.8.3 Comorbidity

Patients who have been cured of testicular cancer have approximately a 2% to 5% cumulative risk of developing a cancer in the opposite testicle during the 25 years after initial diagnosis. Within this range, men with nonseminomatous primary tumors appear to have a lower risk of subsequent contralateral testis tumors than men with seminomas.

HIV-infected men are reported to be at increased risk for developing testicular germ cell cancer. Depending on comorbid conditions such as active infection, these men are generally managed similarly to non-HIV-infected patients.
Because the majority of testis cancer patients who receive chemotherapy are curable, it is necessary to be aware of possible long-term effects of platinum-based treatment, such as the following:

1. Fertility: Many patients have oligospermia or sperm abnormalities prior to therapy. Virtually all become oligospermic during chemotherapy. Many recover sperm production, however, and can father children, often without the use of cryopreserved semen. In a population-based study, 70% of patients actually fathered children. The likelihood of recovering fertility is related to the type of treatment received. The children do not appear to have an increased risk of congenital malformations.

2. Secondary leukemias: Several reports of elevated risk of secondary acute leukemia, primarily nonlymphocytic, have appeared. In some cases, the risks were associated with the prolonged use of alkylating agents or with the use of radiation. Etoposide-containing regimens are also associated with a risk of secondary acute leukemias, usually in the myeloid lineage, and with a characteristic 11q23 translocation. Etoposide-associated leukemias typically occur sooner after therapy than alkylating agent-associated leukemias and often show balanced chromosomal translocations on the long arm of chromosome 11. Standard etoposide dosages (<2 g/m^2 cumulative dose) are associated with a relative risk of 15 to 25, but this translates into a cumulative incidence of leukemia of less than 0.5% at 5 years. Preliminary data suggest that cumulative doses of more than 2 g/m^2 of etoposide may confer higher risk.

3. Renal function: Minor decreases in creatinine clearance occur (about a 15% decrease, on average) during platinum-based therapy, but these appear to remain stable in the long term and without significant deterioration.

4. Hearing: Bilateral hearing deficits occur with cisplatin-based chemotherapy, but the deficits generally occur at sound frequencies of 4 kHz to 8 kHz, which is outside the range of conversational tones; therefore, hearing aids are rarely required if standard doses of cisplatin are administered.

Although bleomycin pulmonary toxic effects may occur, it is rarely fatal at total cumulative doses of less than 400U. Because life-threatening pulmonary toxic effects can occur, the drug should be discontinued if early signs of pulmonary toxic effects develop. Although decreases in pulmonary function are frequent, they are rarely symptomatic and are reversible after the completion of chemotherapy. Reportedly, men treated curatively for germ cell tumors with cisplatin-based regimens have had elevations in total serum cholesterol. This could not be confirmed, however, in another study.

Radiation therapy, often used in the management of pure seminomatous germ cell cancers, has been linked to the development of secondary cancers, especially solid tumors in the radiation portal, usually after a latency period of a decade or more. These include melanoma and cancers of the stomach, bladder, colon, rectum, pancreas, lung, pleura, prostate, kidney, connective tissue, and thyroid. Chemotherapy has also been associated with an elevated risk of secondary cancers.

Oligospermia or sperm abnormalities prior to therapy are common. Radiation therapy, used to treat pure seminomatous testicular cancers, can cause fertility problems because of radiation scatter to the remaining testicle during radiation therapy to retroperitoneal lymph nodes as evidenced in the SWOG-8711 trial, for example. Depending on scatter dose, sperm counts fall after radiation therapy but may recover over the course of 1 to 2 years. Shielding techniques can be used to decrease the radiation scatter to the remaining normal testicle. As with treatment with chemotherapy, some men have been reported to father children after radiation treatment of seminoma, and the children do not appear to have a high risk of congenital malformations.

3.8.4 Therapy

Radiation therapy and/or chemotherapy for patients with testicular cancer may be associated with an increase in cardiovascular morbidity. In a retrospective series of 992 patients treated for testicular cancer at the Royal Marsden Hospital between 1982 and 1992, cardiac events were increased approximately 2.5-fold in patients treated with radiation therapy and/or chemotherapy compared with those who underwent surveillance after a median of 10.2 years. The actuarial risks of cardiac events were 7.2% for patients who received radiation therapy (92% of whom did not receive mediastinal radiation therapy), 3.4% for patients who received chemotherapy (primarily platinum-based), 4.1% for patients who received combined therapy, and 1.4% for patients who underwent surveillance management after 10 years of follow-up. A population-based retrospective study of 2,339 testicular cancer survivors in the Netherlands, treated between 1965 and 1995 and followed for a median of 18.4 years, found that the overall incidence of coronary heart disease (i.e., myocardial infarction and/or angina pectoris) was increased 1.17 times (95% confidence interval , 1.04–1.31) compared with the general population. Patients who received radiation therapy to the mediastinum had a

2.5-fold (95% CI, 1.8–3.4) increased risk of coronary heart disease, and those who also received chemotherapy had an almost 3-fold (95% CI, 1.7–4.8) increased risk. Patients who were treated with infradiaphragmatic radiation therapy alone had no significantly increased risk of coronary heart disease. In multivariate Cox regression analyses, the older chemotherapy regimen of cisplatin, vinblastine, and bleomycin (PVB), used until the mid 1980s, was associated with a significant 1.9-fold (95% CI, 1.2–2.9) increased risk of cardiovascular disease (i.e., myocardial infarction, angina pectoris, and heart failure combined).

The newer regimen of bleomycin, etoposide, and cisplatin (BEP) was associated with a borderline significant 1.5-fold (95% CI, 1.0–2.2) increased risk of cardiovascular disease.

Although testicular cancer is highly curable, all newly diagnosed patients are appropriately considered candidates for clinical trials designed to decrease morbidity of treatment while further improving cure.

3.8.5 Statistics

Estimated new cases and deaths from testicular cancer in the United States in 2008: 1
New cases: 8,090.
Deaths: 380.

4 COST IMPACT

In this section we analyze the costs of the eight cancers we have targeted. The costs are divided into two areas: Initial Treatment, which is the surgical and chemotherapy treatment required at the time of recognition, and second, Ongoing Treatment, the costs associated with treating the remaining set of patients, those surviving over a five year period.

4.1 METHODOLOGY

The process is as follows:

1. Incidence Patients: We use the data base from NCI to determine the incidence and then project going forward on a census basis the total number of cases per year of the eight cancers.

2. We then assign costs for surgery, hospital based, then medications, generally chemotherapy, and then for ongoing physician care. We have not included radiation therapy but that may be factored into a loaded pharmaceutical base.

3. We then calculate the costs for the first year incidence patient base.

4. We then use the mortality rates and then linearize a Kaplan Meir survival curve. Using that we determine over the year 2 through year 5 the number of patients requiring ongoing care.

5. We then assume that we have a similar costs base of physician care and pharmaceuticals over this period.

6. We then combine the results into a total cost profile using constant 2008 dollars and a growing population base. The costs of procedures and pharmaceuticals are derived from the data we have presented in the Health Care White Paper in January 2009.

4.2 COST ELEMENTS

The cost elements in 2008 dollars are contained in the following Table. We include full surgical and surgical related costs for the first year only. We assume ongoing care by a physician trained to deal with the specific cancer and we also assume that some form of chemotherapy is used.

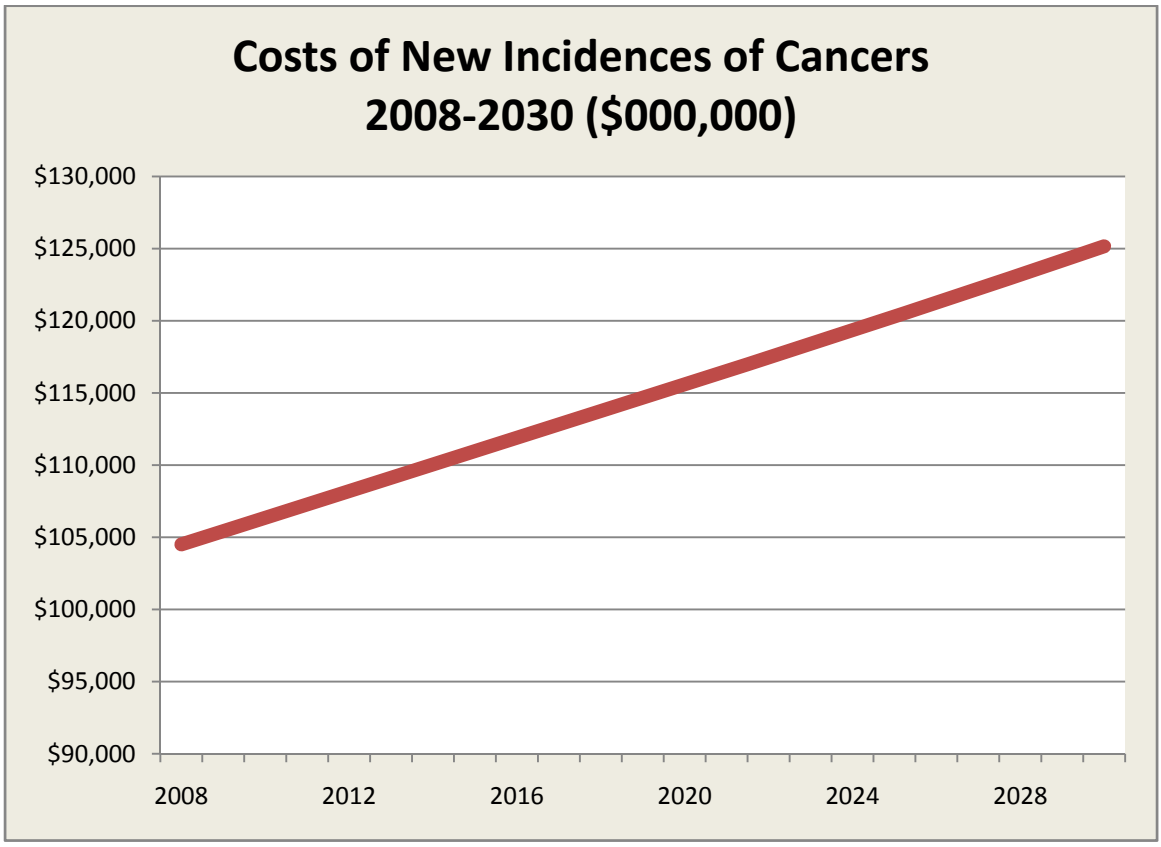
We also assume that in the ongoing years we require medical and chemotherapy help.

	Prostate	*Female Breast*	*Lung and Bronchus*	*Colon and Rectum*	*Melanomas of the Skin*	*Ovary*	*Cervix*	*Testis*
Surgery	$55,000	$75,000	$105,000	$125,000	$55,000	$95,000	$55,000	$75,000
Medication	$15,000	$25,000	$18,000	$20,000	$15,000	$45,000	$15,000	$55,000
Physician	$12,000	$22,000	$25,000	$20,000	$15,000	$25,000	$15,000	$30,000
Total	$82,000	$122,000	$148,000	$165,000	$85,000	$165,000	$85,000	$160,000

4.3 SPECIFIC COST ANALYSES

We now present the financial data for costs. The Figure below is the costs for just new incidences of the eight cancers from 2010 to 2030 in 2008 dollars.

The Figure below shows the total first year costs growing from $105 billion in 2008 and reaching $125 billion in 2030. This may be further increased by age adjustments in the population. However the age changes are problematic because we also see major ethnic changes as well and this distribution in the incidences may see a considerable mix when all of these factors are combined. The Figure below thus represents a reasonable projection going forward.



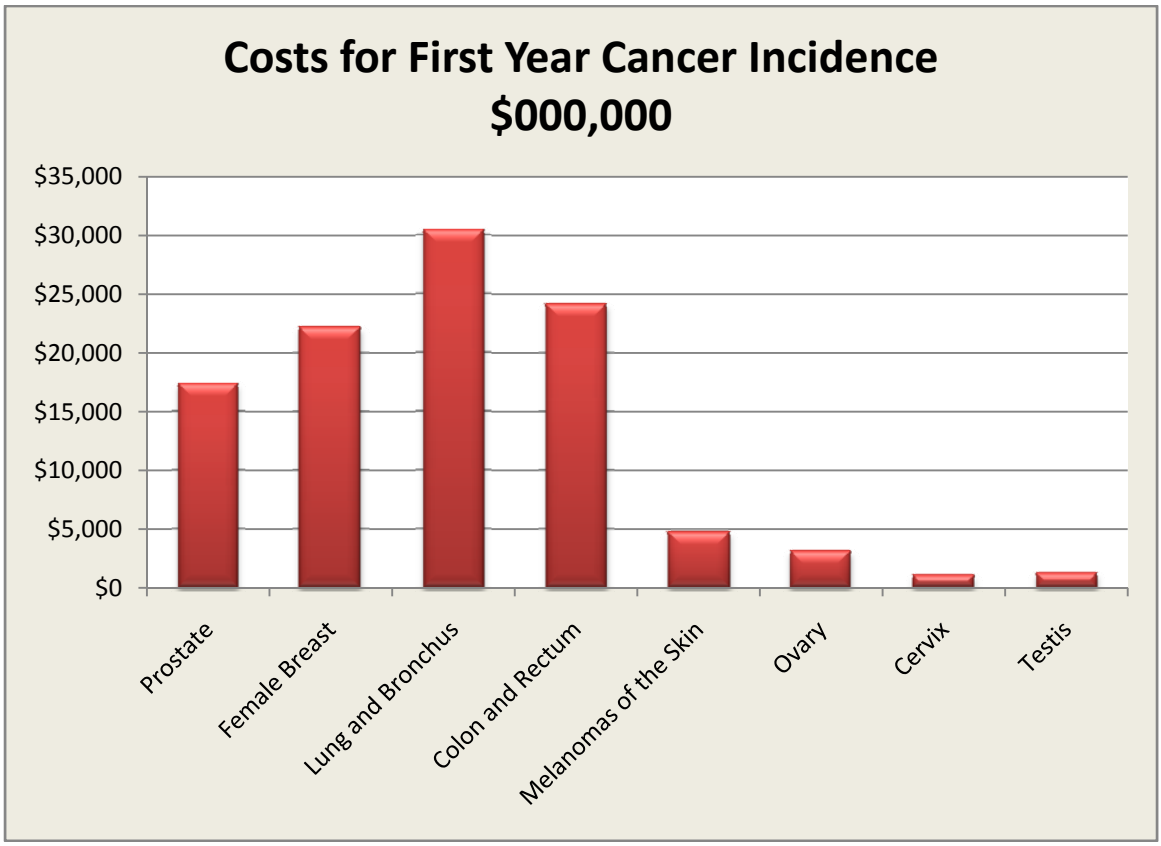
The Table shown below is a detailed breakout for each of the cancers in each of the years in question.

As we have stated earlier it is necessary to have female and male populations since many of the cancers are sex related. The incidences are the incidences in the related affected group and do not represent incidences over the total population. We have assumes a static male and female ratio. Any changes there would be expected to be immaterial over this time horizon.

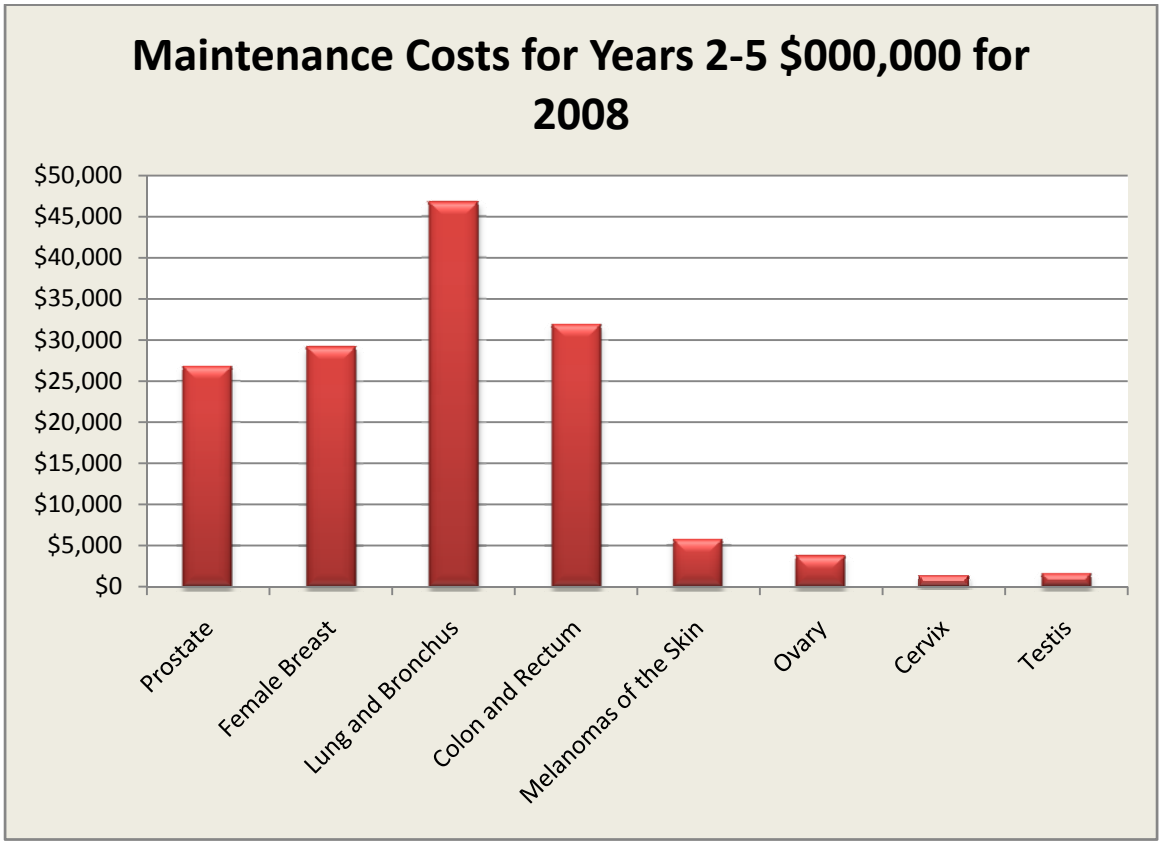
We have also assumed that the treatments do not change in this twenty year period for better or worse. That frankly is a massive assumption as we have discussed earlier. This is the problem with all projections of this nature. In our report on Diabetes it may be reasonable to assume that there will be some genetic work here as well. Yet the understanding of many of these cancers may be quite impressive over this time frame.

Year	*Male*	*Female*	*Total*	*Prostate*	*Female Breast*	*Lung and Bronchus*	*Colon and Rectum*	*Melanomas of the Skin*	*Ovary*	*Cervix*	*Testis*
2008	148,762,847	154,834,799	303,597,646	211,838	182,241	205,536	146,638	56,166	19,200	12,542	8,033
2009	150,073,474	156,198,921	306,272,395	213,705	183,846	207,346	147,930	56,660	19,369	12,652	8,104
2010	151,378,435	157,557,146	308,935,581	215,563	185,445	209,149	149,216	57,153	19,537	12,762	8,174
2011	152,684,431	158,916,449	311,600,880	217,423	187,045	210,954	150,503	57,646	19,706	12,872	8,245
2012	153,997,738	160,283,360	314,281,098	219,293	188,654	212,768	151,798	58,142	19,875	12,983	8,316
2013	155,316,028	161,655,457	316,971,485	221,170	190,268	214,590	153,097	58,640	20,045	13,094	8,387
2014	156,637,123	163,030,475	319,667,598	223,051	191,887	216,415	154,399	59,139	20,216	13,205	8,458
2015	157,959,236	164,406,551	322,365,787	224,934	193,507	218,242	155,703	59,638	20,386	13,317	8,530
2016	159,280,690	165,781,943	325,062,633	226,816	195,125	220,067	157,005	60,137	20,557	13,428	8,601
2017	160,600,243	167,155,354	327,755,597	228,695	196,742	221,891	158,306	60,635	20,727	13,540	8,672
2018	161,917,492	168,526,369	330,443,861	230,571	198,356	223,710	159,604	61,132	20,897	13,651	8,744
2019	163,232,249	169,894,790	333,127,039	232,443	199,966	225,527	160,900	61,629	21,067	13,761	8,815
2020	164,544,228	171,260,318	335,804,546	234,311	201,573	227,340	162,194	62,124	21,236	13,872	8,885
2021	165,859,855	172,629,645	338,489,500	236,184	203,185	229,157	163,490	62,621	21,406	13,983	8,956
2022	167,185,597	174,009,498	341,195,095	238,072	204,809	230,989	164,797	63,121	21,577	14,095	9,028
2023	168,521,475	175,399,903	343,921,378	239,975	206,446	232,835	166,114	63,625	21,750	14,207	9,100
2024	169,867,835	176,801,217	346,669,052	241,892	208,095	234,695	167,441	64,134	21,923	14,321	9,173
2025	171,225,208	178,213,991	349,439,199	243,825	209,758	236,570	168,779	64,646	22,099	14,435	9,246
2026	172,592,106	179,636,682	352,228,788	245,771	211,432	238,459	170,127	65,162	22,275	14,551	9,320
2027	173,967,328	181,068,036	355,035,364	247,729	213,117	240,359	171,482	65,682	22,452	14,667	9,394
2028	175,352,231	182,509,464	357,861,695	249,702	214,814	242,272	172,847	66,204	22,631	14,783	9,469
2029	176,748,213	183,962,425	360,710,638	251,689	216,524	244,201	174,223	66,731	22,811	14,901	9,544
2030	178,156,373	185,428,062	363,584,435	253,695	218,249	246,147	175,611	67,263	22,993	15,020	9,620

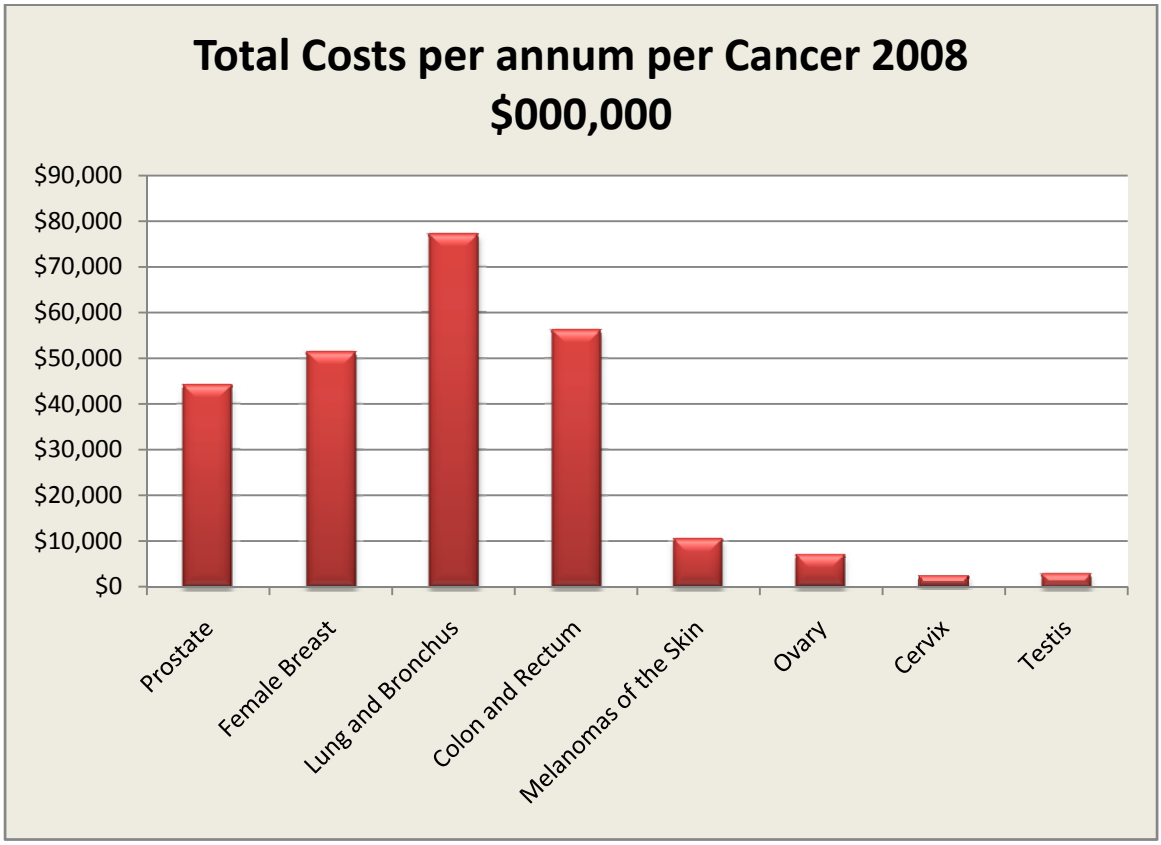
The following Figure is a detailed close-up of the separate costs of the first year incidence. The key observation is that lung has the highest amount but it also has the lowest survival. This maintenance should be expected to be somewhat lower.



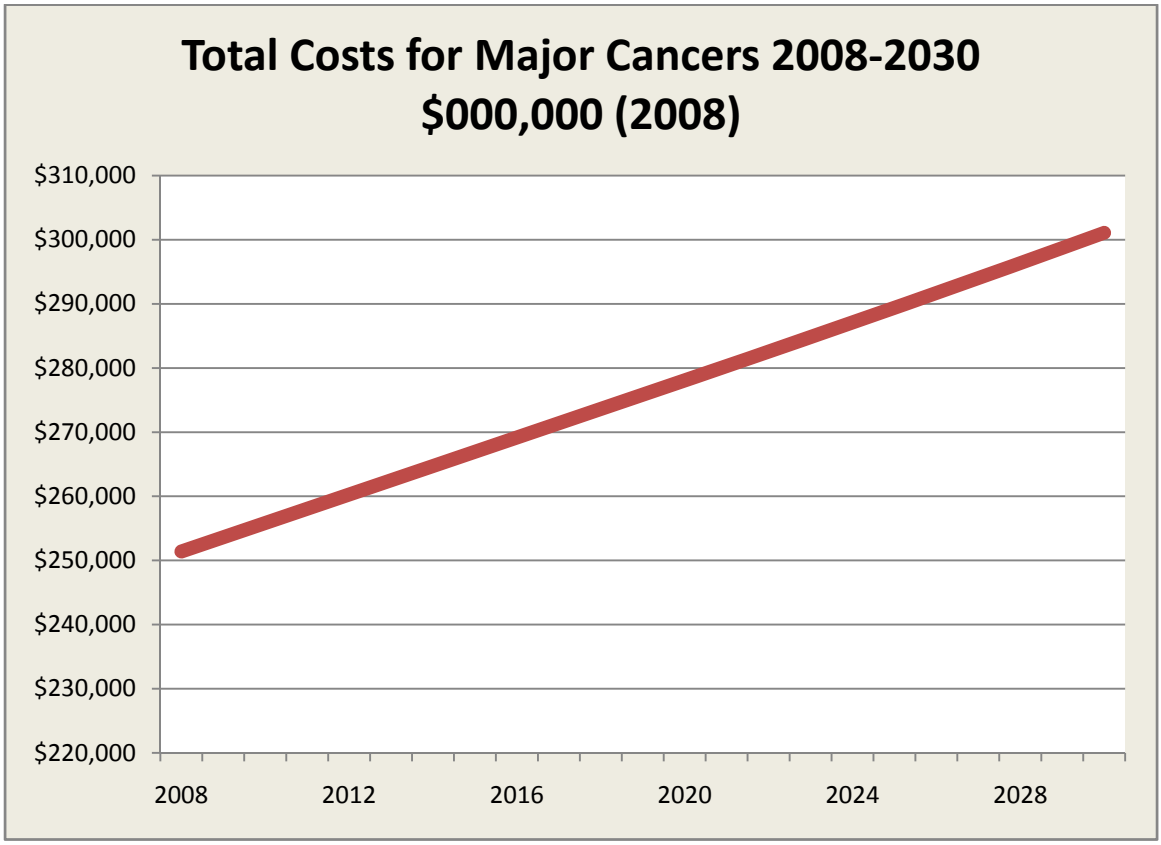
We have the maintenance costs her. What is a both surprising are the costs or four year maintenance of lung cancer. Here we have the costs for all people who have had the disease for 2, 3, 4, 5, years. This includes taking into account the losses due to deaths.



The following Figure is thus the sum of the two for 2008 by disease. Lung cancer dominates at $80 billion direct costs. This has always been a known fact. The incidence of this may decrease in the event of continued downward pressure on cigarette smokers.



Finally we present in the following Figure the total costs for treatment of these eight cancers. Note than in 2008 it is $250 billion and this is more than 10% of all health care costs. As we have said previously, by controlling these, type 2 Diabetes, and secondary effects of cigarettes smoking we can reduce health care by almost 25% from its current run rate.



Thus from the above summary chart we see that these eight cancers which we argue are controllable contribute more than 10% of the total expenditures for health care. As we had shown in the Type 2 Diabetes paper that constitutes another 10-12% and cigarette smoking effects aside from lung cancer, such as heart and emphysema add another 6-7%. This in total is almost 25% of the total amount. We find it amazing how the totality of plans fails to address the demand issue which we have been looking at. They all seem to worry about how to pay for it not how to reduce the demand.

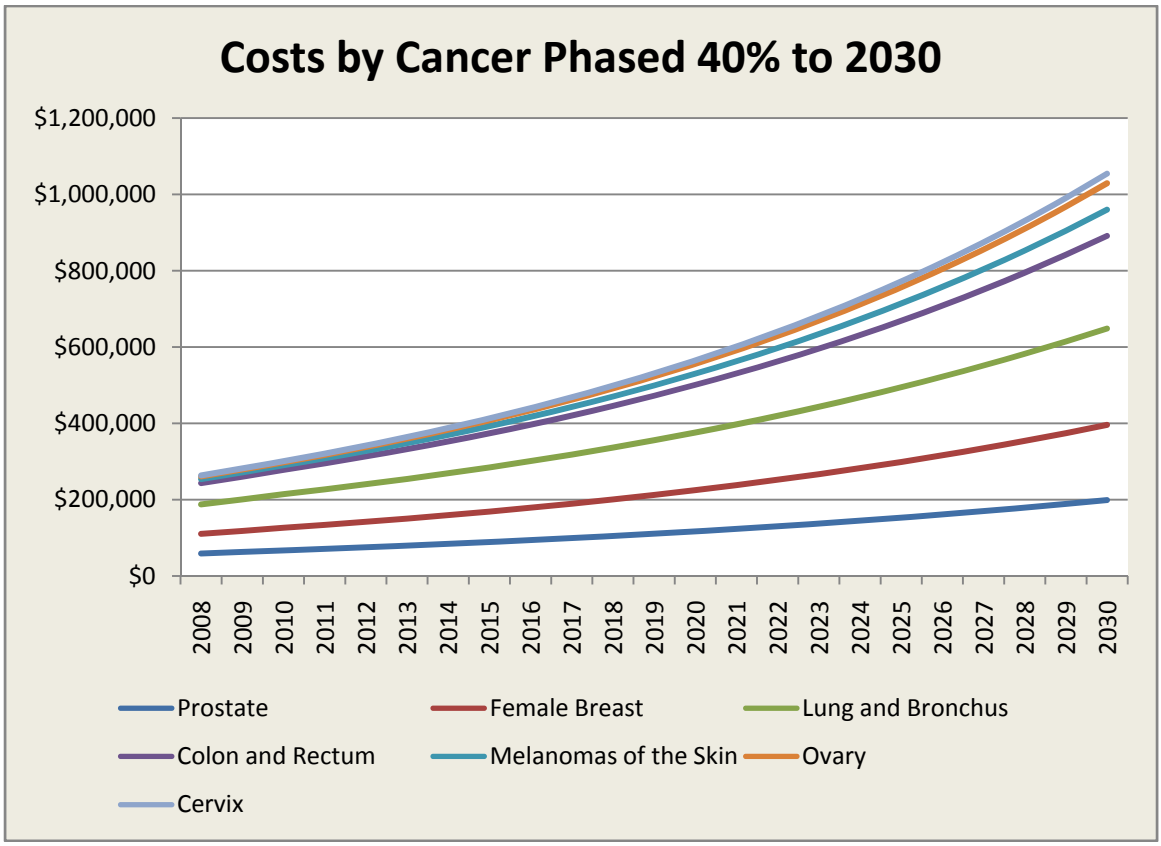
4.4 IMPACT OF CONTROLLABILITY

We can now consider the impact of controllability. We assume that if we can remediate by taking the actions in diagnosing early and reducing any substantial surgery or by diagnosing early and having minimal surgery that we can reduce the costs dramatically. We have performed that analysis herein.

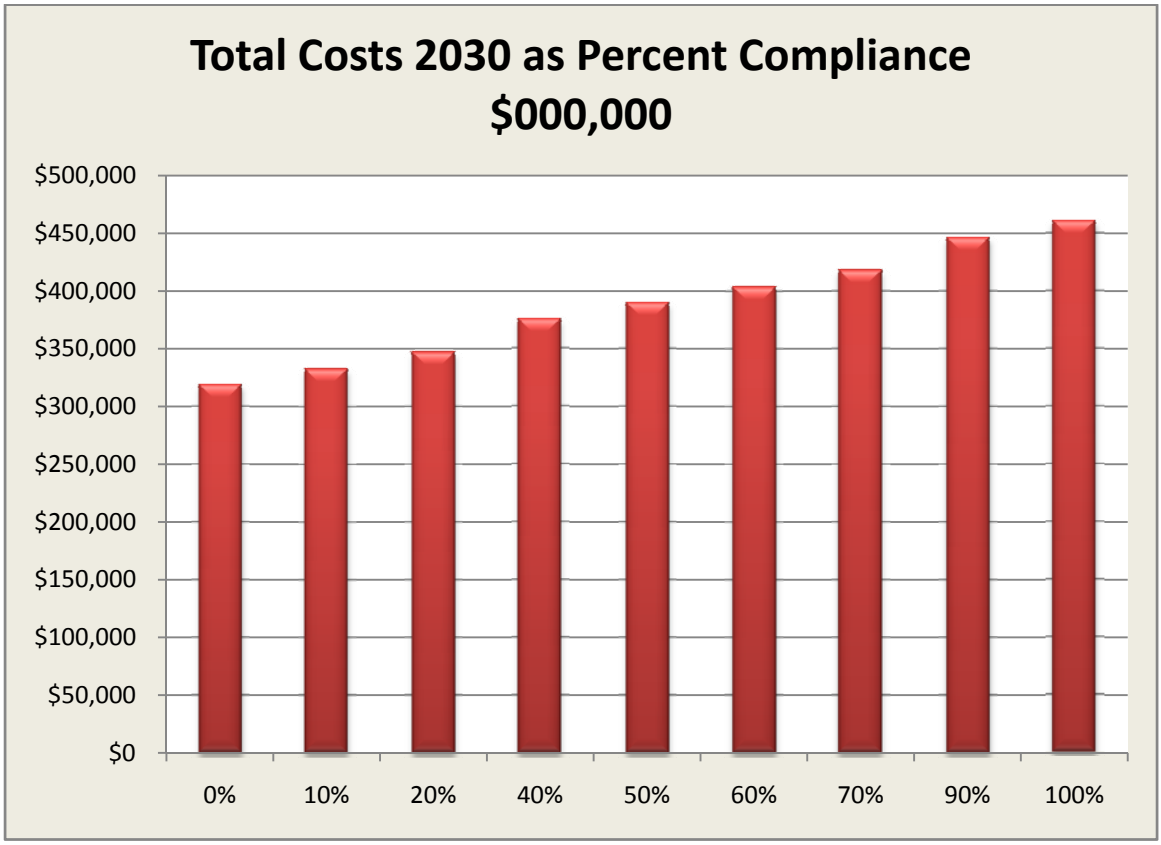
In this analysis we phase in a system of screening and remedial treatment for screened patients and phase it in over this period linearly. We used standard 2008 dollar costs for screening and then we use remediation costs as discussed.

The following Figure depicts the costs per year as we vary pre-screening compliance. It must be remembered that there are still surgical costs because of breast surgery, skin

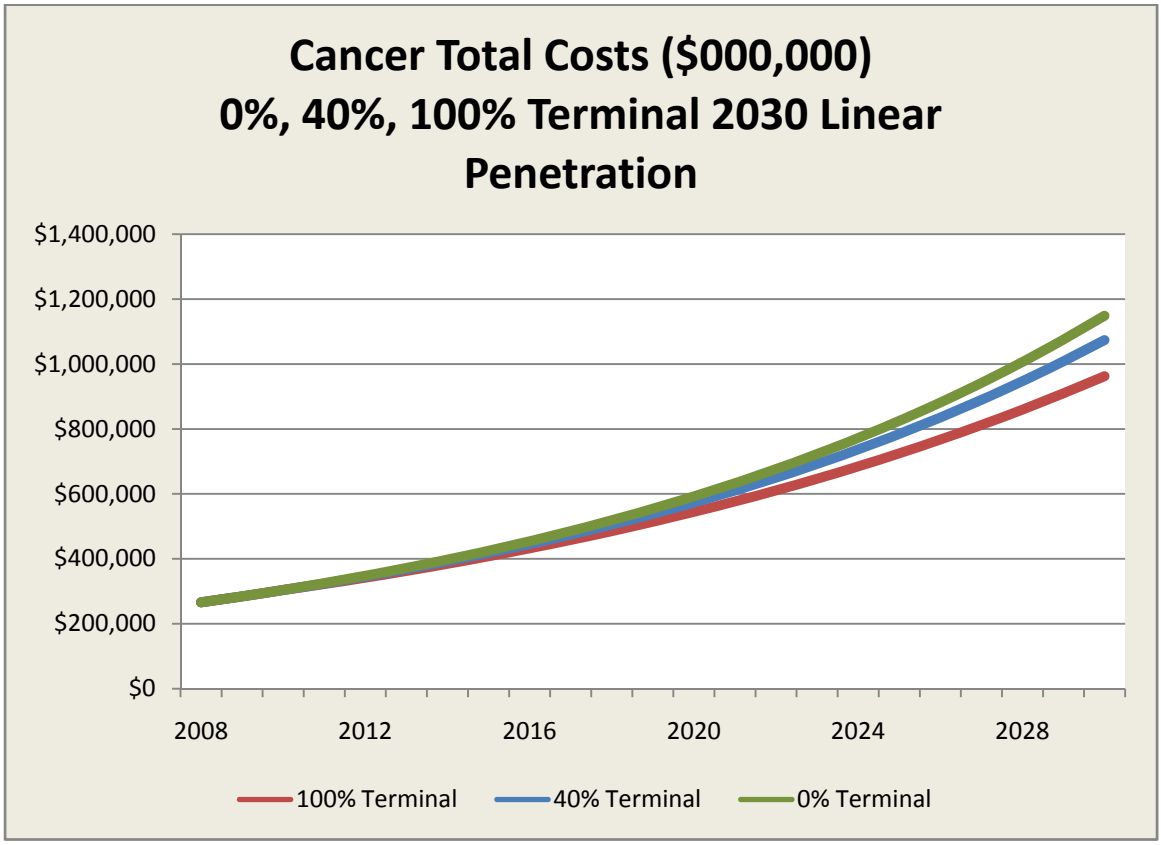
excisions and the like but that the costs are lower and the ongoing maintenance is also substantially lower due to low rates of metastases. There is a substantial savings in all of these plans. The most likely scenario is a phased introduction on compliance and thus we would expect the high amount early on and then the lowering to the lower scales.



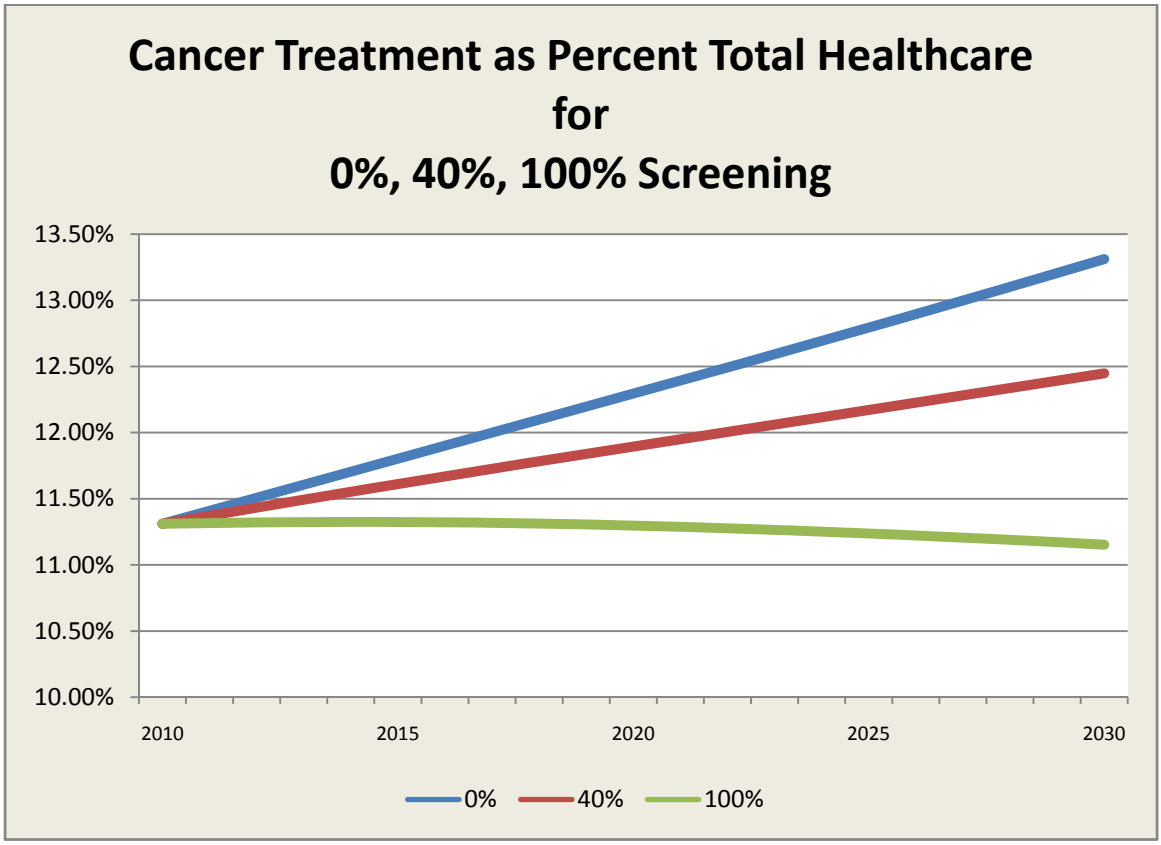
The following looks at 2030. This makes clear the impact in that year of the use of compliance, a factor of 15% reduction in costs despite the increase in population by 40%. However this analysis still assumes that no medical advances are made in this twenty year period, no genetic therapies are achieved. We recognize that that assumption is at its core false and thus we would anticipate even further savings.



Finally we look at three scenarios. They are for 0%, 40%, 100% remediation linearly over 2010 to 2030. The result is shown below.

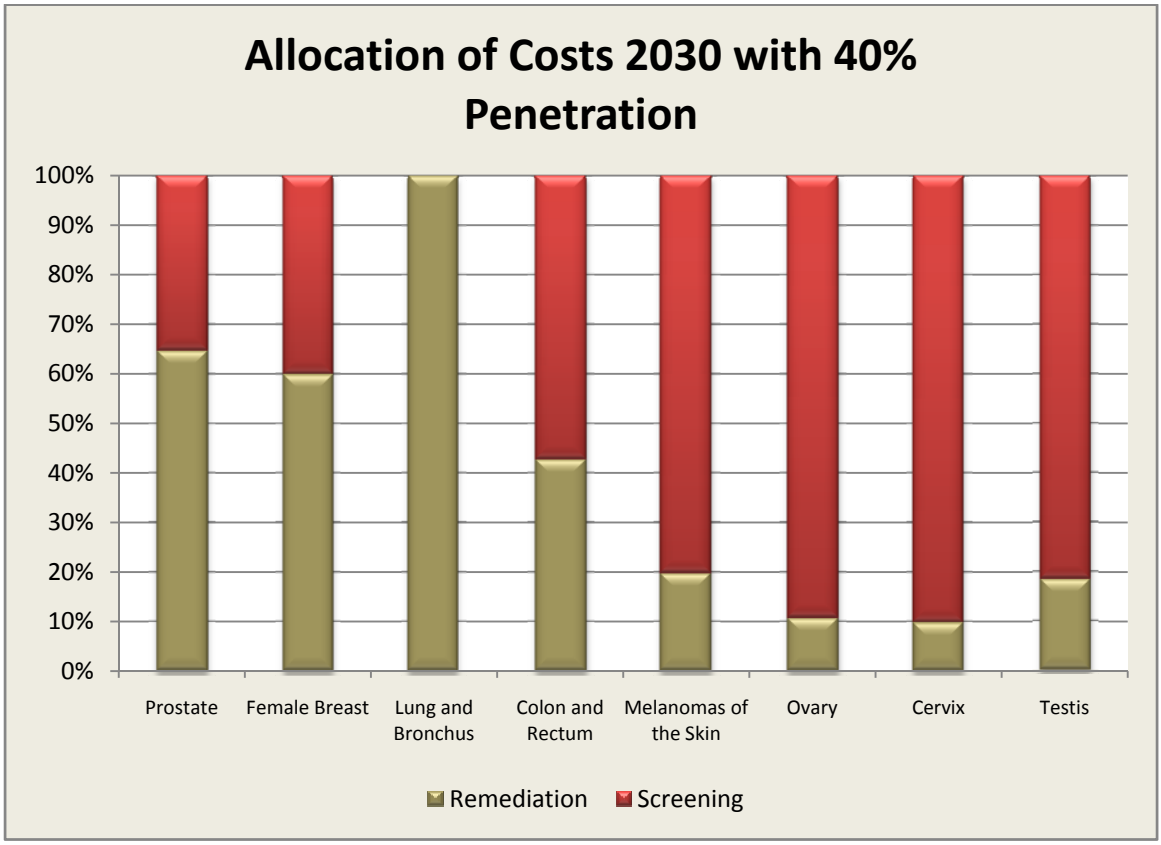


We then show it as a percent of total costs in that year. Note the decrease as we screen.

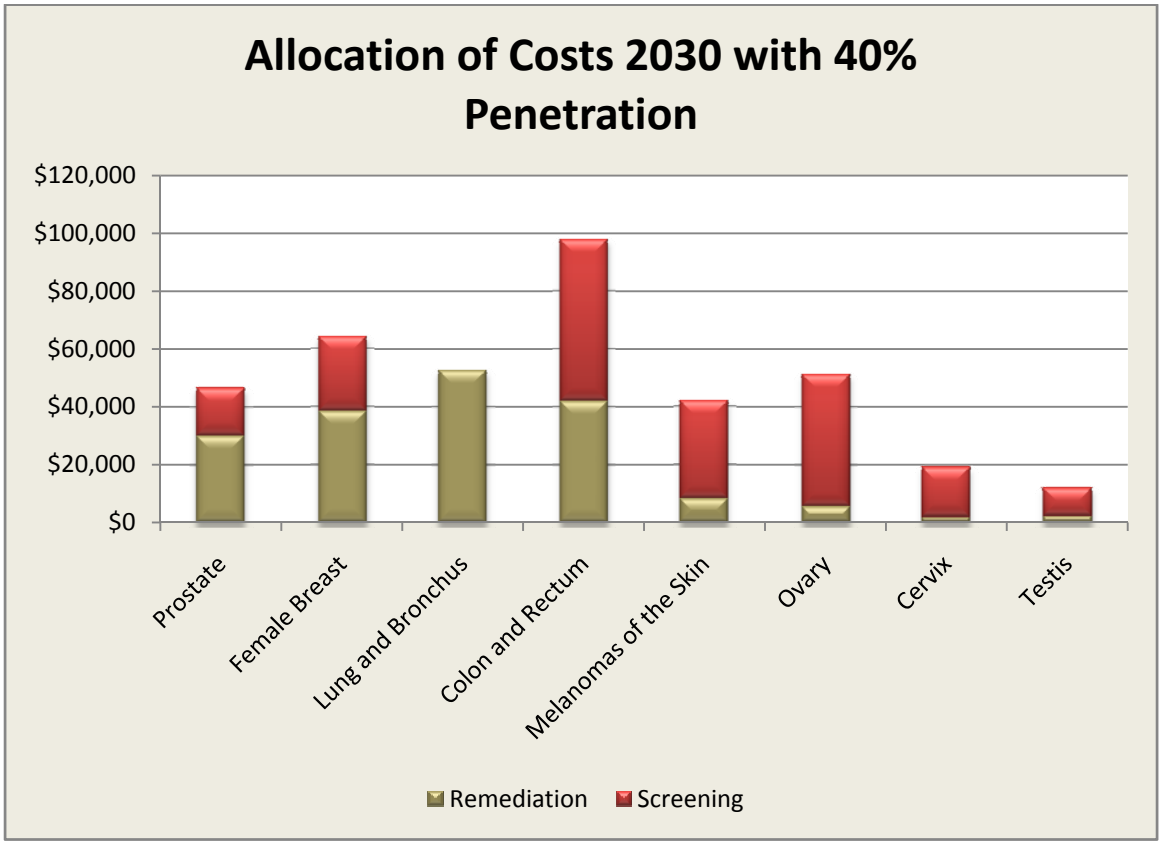


Note that the no remediation grows from $250 billion to over $300 billion. The 40% plan shows some reduction in rate of growth. The 100% compliance plan shows almost a flat profile in cost despite a 40% increase in population.

The following Figure shows an example of the costs per disease and by percent for each part, treatment, screening or remediation.



Note in the above that the ratio of screening to remediation is a metric of interest. We show that detail below.



Here we see that the prostate, colon and breast cancers have a good screening to remediation ratio. That is there is a high incidence and high costs per incidence. Screening is done over all the population and remediation on this with incidence. In contrast treatment is done only on those with incidence and frequently since screening is not performed the treatment is considerably more costly than remediation. This is a bit more complex. For example in melanoma screening can recognize a lesion at low costs and result in a low cost of removal. Thus the high screening cost percent is really a low screening cost in total. The ovary cancers are by far more costly since remediation requires surgery, albeit less complicated. The cervical case is more akin to melanoma.

4.5 REMEDIATION PLAN

The next question is how do we achieve this controllable position. Namely what will motivate a patient to seek out the controllable options necessary to achieve the reductions? This is an economic as well as psychological issue.

Economically we can propose that we compensate a patient for having sought a controllable disease evaluation by having some form of rebate. The opposite which is a penalty on health care premiums is a negative approach. Either way it results in a sloping demand curve.

The second issue is that of psychological control. The major problem, even in universal health care, is patient participation. For example, colonoscopies can be life saving yet patient at high risk, say having multiple first degree relatives with colon cancer, refrain from being tested. This is due to fear, dislike of the test procedure, embarrassment and many other factors which are independent of cost or availability. It may also be cultural. Thus besides a financial motivator, a pure economic solution, some form of persuasion or education is essential.

5 CONCLUSIONS AND RECOMMENDATIONS

This study has focused on potentially remediable cancers which can be caught early and that the risk of mortality and severe morbidity can be reduced. However this study has raised several key issues, and there are recommendations related thereto.

1. Medical practice is a continuing evolving process and the prediction of the future based solely on the past is fraught with errors and distortion. The preponderance of health care plans and analyses fail to account for anticipated changes in the practice of medicine and this failure results in significant projection errors in costs as well as significant errors in the structures used for the servicing of the patients.

2. Genetic techniques for determining susceptibility, existence, staging, and prevention may very well be the key advances over the next twenty years and as such their effects may dramatically outweigh the impacts of cost reduction. As such the allocation of funds into these areas and the use of highly focused research in these areas will have payoffs which could be highly exceptional in the long run.

3. The patient's willingness to accept responsibility for their own care is fundamentally at the core of improving health care in the United States. Whether from fear, ignorance, or whatever the reason, patient compliance with medical advice and control of life style as well as the patient's adherence to screening regimes will be an essential part of any plan achieving its goal.

4. There is a changing set of paradigms in the delivery of medicine with the expansion of genetic based care. This paradigm shift will require changes in the way health care can and should be provided and may likely result in the distribution of health care delivery assets.

5. There are a set of controllable cancers which can be managed with the tools that exist today and which are highly likely to be addressed by the genetic techniques which are evolving. The set of such cancers today represent a significant number of all cancers in totality. It is anticipated that this will continue to expand.

6. Physician education must be expanded on a continuing basis to motivate patients to be screened using current techniques as well as being prepared to more widely disseminate the genetic techniques as they evolve.

7. Government spending should focus on a strategic set of genetic medical goals in the areas of screening, staging and prevention, and this focus should be a broadly based approach on the most impacted cancers to demonstrate that the genetic applications are the most efficacious.

8. The changes in the practice of medicine for this class of disease using genetic methods may alter the nature of the relationships between the existing players; physicians, hospitals, drug manufacturers, and Government. There is a natural tendency to maintain the status quo in a set of power relationships. If genetic treatments can be performed extra a hospital based environment than the hospitals may be reduced to institutions to deal with chronic care, and acute care for those requiring immediate support only provided by that environment. There may very well be strong institutional resistance to these changes.

9. Genetic medicine will suffer great regulatory lag. The FDA and other regulatory entities generally have a slow and aged process to deal with drugs and lack fundamental understandings of the new genetic treatments. This will result is massive regulatory lag in releasing treatments.

10. The proposed Comparative Clinical Effectiveness, Evidence Based Medicine, and similar movements will also create a slowness in adoption of new therapeutic measures. They will create methods and processes that will demand long duration testing and evaluation of any new procedure and process thus prolonging introduction, increasing and sustaining costs and causing increased mortality and morbidity.

11. The use or remedial screening of patients for targeted cancers can have a dramatic effect on overall health care costs, reducing them by a factor of 3 ore even more. However those numbers assume the practice of medicine on an as is basis and does not factor in any new diagnostic or treatment options as would be anticipated with the inclusion of genetic methods and techniques.

12. With the introduction of genetic medicine to diagnosis, treat and prevent large sets of what can be controllable diseases, using the cancer set discussed herein, the impact of this new treatment regimen will result in a significant structural change in the delivery of healthcare. As psychiatric hospitals went through massive shifts in the late 1960s and early 1970s with the introduction of psychiatric drugs such as haloperidol and the like, setting out many patients into the outside world now controlled by drugs, it is possible that the current hospital system may go through a similar shift.

6 APPENDIX A WORLD VIEW

We spend a few thoughts in this appendix on the concept of architecture and world view. The "architecture" of health care is the set of "instruments" which are used to diagnosis and treat disease. The western world has evolved a view of medicine as composed of the diagnostic and treatments tools, methods, procedures and their interrelationships which in their totality constitute what we call the health care system. These elements and their inter-relationships are the architecture.

They are predicated on paradigms or examples which we rely upon for validating this collection of interconnecting elements in our minds as a holistic and believable effort with the end goal of providing good the people treated in its confines. However it is often worthwhile to step back and examine these elements and to reassess what is being done is being done in a manner which meets the overall goals and is evolutionary can changes to permit new methods, techniques, elements and processes. Furthermore by stepping back we may have the opportunity to glimpse at the possibility of creating and introducing new and more efficacious elements into the world.

We will argue that comparative clinical effectiveness and evidence based medicine are nominal extensions of the current architecture of medicine based on existing paradigms and embedded in the well established world views. The problem that these two approaches may have is that they may tend to reinforce this existing and possibly soon to be outmoded viewpoint.

Politicians and policy makers all too frequently, and in my opinion almost always, look backward, repairing the inefficiencies of the past if possible and promoting the interests of the present. They do not, and more than likely lack the ability to, look forward. However it is incumbent upon the medical profession to do so. The introduction of genetic methods and techniques as related to diagnosis and treatment will be earth shattering. This section lays a bit of a philosophical framework for that effort.

The concept of an architecture of the disease process has been an unarticulated but inherent cornerstone in the development of medical care. That medical architecture has a set of elements, beliefs, preconceptions, processes, procedures, rituals and the like. It is to some degree scientifically and evidenced based. It has the diagnostic criteria, along with the tests and procedures, and the treatment protocols. It also includes how these are developed and vetted. However, the structural elements of these architectures have often not played a role in the development of policies. In this section we will briefly look at the concept of an architecture as a means to understand the issue of health care and will provide a new set of perspectives for viewing health care in terms of a new paradigms and world views.

An architecture, first, requires that the underlying system be treated in terms of a set of commonly understood elements and that these elements have a clearly demarcated set of functions and interfaces that allow for the combining of the basic set of elements. The way the elements then can be combined, reflected against the ultimate types of services provided, determine the architecture. In health care these elements are the diagnostic tools and procedures and the treatment protocols.

An architecture, secondly, is driven by two factors; technology and world view. Technology places bounds on what is achievable, however those bounds are typically well beyond the limits that are self-imposed by the designer or architect in their view of the user in their world. This concept of architecture and the use of design elements are critical in understanding the paradigms used in the structure of information systems. World view is the more powerful driver in an architecture. We argue in this paper that it is essential to develop a philosophical perspective and understanding of how to view networks. We argue with Winograd and Flores, and in turn with Heidegger, that we must be thrown into the network, to understand the needs of the users, and to understand the structure of the paradigms that are used to construct the world view.

To better understand the importance of an architecture we develop the concept of the historicity of architectures based upon the work of Kuhn and ten that of McLuhan. Kuhn begins his thesis of how scientific revolutions occur by the introduction of the concept of paradigms. Kuhn defines these as;"...the term paradigm is used in two different senses. On the one hand, it stands for the entire constellation of beliefs, values, and techniques, and so on shared by the members of a given community. On the other, it denotes one sort of element in that constellation, the concrete puzzle-solutions which, employed as models or examples, can replace explicit rules as a basis for the remaining puzzles of normal science, The first sense of the term, call it sociological, ..., “

The concept of a paradigm is in essence the collection of current technologies that we have at hand for the network and the ways we put these elements together. New paradigms result from new technologies. New technologies allow for the placing of the elements together in new ways. Kuhn, then goes on to demonstrate that the world view, that is how we view ourselves and our environment is based upon the our acceptance of these paradigms, as either collections of techniques and technologies or as collections of embodiments of these techniques and technologies in "examples". We then end to accept this as the way things are and should be.

Then Kuhn argues, as the technologies change, changes in the paradigms do not occur in a continuous fashion but almost in quantum leaps. The new paradigms build and congeal until they burst forth with new world views. It is this model that we ague applies to the evolution of broadband.

It is this philosophical view, almost Hegelian in form that is essential in understanding the underlying and formative changes in paradigms that will change our world view.

As a second perspective of the impact of technology as a dominant driver, we can refer to McLuhan and his development of the concept of media. Drucker has referred to the presentation of McLuhan's doctoral thesis and McLuhan is quoted as follows (See Drucker, p. 250):

"Movable type, rather than Petrarch, Copernicus, or Columbus was the creator of the modern world view..."Did I hear you right," asked one of the professors as McLuhan had finished reading, "that you think printing influenced the course s the universities taught and the role of the university, altogether?" "No, sir," said McLuhan, "it did not influence; printing determined both, indeed, printing determined henceforth what was going to be considered knowledge."

This concept later evolved into the medium being the message. In our context it is the fact that both Kuhn and McLuhan recognized, albeit in differing fields and in differing ways, that fundamental changes in technology and technique, call it paradigm or the medium, will change the world view, also the message.

It is the importance of understanding the change in the technology, its function and evaluates the possible change that this will have in the world view. It will be argued, that much of the thinking in the current diagnostic and staging areas, staging in particular, is based upon possibly outmoded techniques and structures, and that a differing world view will evolve as we introduce genetic based methods and methodologies. We shall develop this construct more fully as we proceed.

The concept of a world view is an overlying concept that goes to the heart of the arguments made in this paper. To better understand what it implies, we further examine several common views and analyze the implications of each. If we view our world as hierarchical, then the diagnostic methods as well as treatment protocols may very well reflect that view. If we further add to that view a bias towards gross physical measurements and realities as compared to genetic elements, these two elements will be reflected in all that we do. The very observations that we make about our environment and the needs of the users will be reflected against that view. As an external observer, we at best can deconstruct the view and using the abilities of the hermenutic observer, determine the intent of the builder.

7 REFERENCES

1. Ackerman, B. et al, Differential Diagnosis in Dermatopathology, Lea and Febiger (Philadelphia) 1988.
2. Amundadottir LT, Sulem P, Gudmundsson J, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006; 38: 652-8.
3. Andreole, G. et al, Mortality Results from a Randomized Prostate Screening Trial, NEJM 360:13 March 2009.
4. Balch, C. et al, Cutaneous Melanoma, Quality (St Louis) 1998.
5. Ballo, MT, Ross, MI, Cormier, JN, et al. Combined-modality therapy for patients with regional nodal metastases from melanoma. Int J Radiat Oncol Biol Phys 2006; 64:106.
6. Binder RL. Neurologically silent brain tumors in psychiatric hospital admissions: three cases and a review. J Clin Psychiatry. 1983 Mar; 44(3):94-7.
7. Buchsbaum, JC, Suh, JH, Lee, SY, et al. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 2002; 94:2265.
8. Cannistra, S., M.D., Cancer of the Ovary, n engl j med 351;24 www.nejm.org December 9 2004
9. Carpenter WR, Robinson WR, Godley PA. Getting over testosterone: postulating a fresh start for etiologic studies of prostate cancer. J Natl Cancer Inst 2008; 100: 158-9.
10. Casado, E. , Transcriptional Targeting for Ovarian Cancer Gene Therapy, Gynecologic Oncology 82, 229–237 (2001)
11. Cavenee WK, Dryja TP, Phillips RA, et al. Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature 1983; 305:779-84.
12. Commonwealth Fund, The Path to a High Performance US Health System, February 2009.
13. Curtin et al, Distinct Sets of Genetic Alterations in Melanoma, New England Journal Med. pp. 353;20 November 17, 2005.
14. DeVita, V., Cancer, Lippincott (New York) 1997.
15. DeVita, V., et al, Cancer, Lippincott (New York) 1997.
16. Drucker, P., Adventures of a Bystander, Harper Row (New York), 1979.
17. Ewend, MG, Carey, LA, Brem, H. Treatment of melanoma metastases in the brain. Semin Surg Oncol 1996; 12:429 February 26, 2004.
18. Ferrone, E et al, Clinicopathological Features of and Risk Factors for Multiple Primary Melanomas, JAMA, October 5, 2005—Vol 294, No. 13 pp. 1647
19. Fife, KM, Colman, MH, Stevens, GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol 2004; 22:1293.

20. Figueiredo, M., et al, Advances in Preclinical Investigation of Prostate Cancer Gene Therapy, Molecular Therapy, vol. 15 no. 6, 1053–1064 June 2007.
21. Foulkes, W., Inherited Susceptibility to Common Cancers, NEJM, November 13, 2008.
22. Freytag, S, et al, Prostate Cancer Gene Therapy Clinical Trials, Molecular Therapy, vol. 15 no. 6, 1042–1052 june 2007.
23. Galasko D, Kwo-On-Yuen PF, Thal L. Intracranial mass lesions associated with late-onset psychosis and depression. Psychiatr Clin North Am. 1988 Mar; 11(1):151-66.
24. Gogas et al, Prognostic Significance of Autoimmunity during Treatment of Melanoma with Interferon , New England Journal Med. pp. 354;7 February 16, 2006.
25. Greenberg DB, Brown GL. Mania resulting from brain stem tumor. J Nerv Ment Dis. 1985 Jul; 173(7):434-6.
26. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007; 39:977-83.
27. Gupta, G, Robertson, AG, MacKie, RM. Cerebral metastases of cutaneous melanoma. Br J Cancer 1997; 76:256.
28. Hagen, NA, Cirrincione, C, Thaler, HT, DeAngelis, LM. The role of radiation therapy following resection of single brain metastasis from melanoma. Neurology 1990; 40:158.
29. Haiman CA, Hsu C, de Bakker PI, et al. Comprehensive association testing of common genetic variation in DNA repair pathway genes in relationship with breast cancer risk in multiple populations. Hum Mol Genet 2008; 17:825-34.
30. Howard, D. et al, The Problem of Brain Tumor in Psychiatric Diagnosis, Am J Psychiatry 98:720-726, March 1942
31. J Foong, M Maier, C A Clark, G J Barker, D H Miller, M A Ron, Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study , J Neurol Neurosurg Psychiatry 2000;68:242-244 (February)
32. Jähnel M. Schizophreniform Psychosis in a Patient with Right Temporal-parietal Meningioma, Psychiatr Prax. 2003 May; 30(Suppl 2):66-69.
33. Johnson, JD, Young, B. Demographics of brain metastasis. Neurosurg Clin N Am 1996; 7:337.
34. Julie Ma, M.D. Mania Resulting From Brain Tumor, UCLA School Medicine, Clinical Vignette, http://www.med.ucla.edu/modules/wfsection/article.php?articleid=120 v
35. Konstadoulakis, MM, Messaris, E, Zografos, G, et al. Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases. Is there a role for surgery? J Neurosurg Sci 2000; 44:211.
36. Krown, SE, Niedzwiecki, D, Hwu, WJ, et al. Phase II study of temozolomide and thalidomide in patients with metastatic melanoma in the brain: high rate of thromboembolic events (CALGB 500102). Cancer 2006; 107:1883.
37. Kuhn, T.S., The Structure of Scientific Revolutions, Univ Chicago Press (Chicago),

1970.
38. Le Marchand L, Donlon T, Kolonel LN, Henderson BE, Wilkens LR. Estrogen metabolism-related genes and breast cancer risk: the Multiethnic Cohort Study. Cancer Epidemiol Biomarkers Prev 2005; 14:1998-2003.
39. Lisanby SH, Kohler C, Swanson CL, Gur RE., Psychosis Secondary to Brain Tumor. Semin Clin Neuropsychiatry. 1998 Jan; 3(1):12-22.
40. Lynch HT, Shaw 1. MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer: study of two large Midwestern kindreds. Arch Intern Med 1966; 117: 206-12.
41. McLuhan, M., The Gutenberg Galaxy, Univ Toronto Press (Toronto), 1962.
42. McLuhan, M., Understanding Media, NAL (New York), 1964.
43. McWilliams, RR, Brown, PD, Buckner, JC, et al. Treatment of brain metastases from melanoma. Mayo Clin Proc 2003; 78:1529.
44. Miller, A., M. Mihm, Melanoma, New England Journal Med pp. 355; 1 July 6, 2006.
45. Moore, R. G., How Do You Distinguish a Malignant Pelvic Mass From a Benign Pelvic Mass? Imaging, Biomarkers, or None of the Above, JOURNAL OF CLINICAL ONCOLOGY. VOLUME 25 _ NUMBER 27 _ SEPTEMBER 20 2007
46. Mori, Y, Kondziolka, D, Flickinger, JC, et al. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. Int J Radiat Oncol Biol Phys 1998; 42:581.
47. Morton, D. et al, Sentinel-Node Biopsy or Nodal Observation in Melanoma, England Journal Med pp. 355;13 September 28, 2006.
48. Radbill, AE, Fiveash, JF, Falkenberg, ET, et al. Initial treatment of melanoma brain metastases using gamma knife radiosurgery: an evaluation of efficacy and toxicity. Cancer 2004; 101:825.
49. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996; 273:1516-7.
50. Rose, P., Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma, n engl j med 351;24 www.nejm.org December 9, 2004
51. Ross, L. et al, Psychiatric, Hospitalizations among Survivors of Cancer in Childhood or Adolescence, NEJM August 14, 2003.
52. Royal College of Obstricians and Gynocologists, OVARIAN CYSTS IN POSTMENOPAUSAL WOMEN, Guideline No. 34 October 2003.
53. Saha, S, Meyer, M, Krementz, ET, et al. Prognostic evaluation of intracranial metastasisin malignant melanoma. Ann Surg Oncol 1994; 1:38.
54. Salvati, M, Cervoni, L, Caruso, R, Gagliardi, FM. Solitary cerebral metastasis from melanoma: value of the'en bloc'resection. Clin Neurol Neurosurg 1996; 98:12.
55. Sampson, JH, Carter, JH Jr, Friedman, AH, Seigler, HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 1998; 88:11.
56. Samuels, M., et al, Office Practice of Neurology, Churchill Livingston (New York) 1996.
57. Sawaya, R, Bindal, RK. Metastatic brain tumors. In: Brain Tumors, Kaye, AH, Laws,

ER Jr (Eds), 1995, Churchill Livingstone, New York 1995. p.923.
58. Schmeler, K., Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome, n engl j med 354;3 www.nejm.org january 19, 2006.
59. Schroder, S, et al Screening and Prostate-Cancer Mortality in a Randomized European Study, NEJM 360:13 March 2009.
60. Selek, U, Chang, EL, Hassenbusch SJ, 3rd, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. Int J Radiat Oncol Biol Phys 2004; 59:1097.
61. Skibber, JM, Soong, Sj, Austin, L, et al. Cranial irradiation after surgical excision of brain metastases in melanoma patients. Ann Surg Oncol 1996; 3:118.
62. Stone, A, Cooper, J, Koenig, KL, et al. A comparison of survival rates for treatment of melanoma metastatic to the brain. Cancer Invest 2004; 22:492.
63. Sun T, Gao Y, Tan W, et al. A six-nucleotide insertion-deletion polymorphism in the CASP8 promoter is associated with susceptibility to multiple cancers. Nat Genet 2007; 39:605-13.
64. Susan Beckwitt Turkel, M.D., David Tishler, M.D. and C. Jane Tavaré, M.S. , Late Onset Psychosis in Survivors of Pediatric Central Nervous System Malignancies, J Neuropsychiatry Clin Neurosci 19:293-297, August 2007
65. Tasman, A. et al, Psychiatry, Saunders (Philadelphia) 1997.
66. TEFFERI,A., Primer on Medical Genomics Part III: Microarray Experiments and Data Analysis, *Mayo Clin Proc*. 2002;77:927-940
67. Thomas et al, Excision Margins in High-Risk Malignant Melanoma, New England Journal Med, pp 350; 8 February 19, 2004.
68. Thompson, J. et al, Melanoma, Martin Dunitz (New York) 2004.
69. Tomlins, S. et al, Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer, Science, Vol 310 October 2005.
70. Tsao et al, Case 6-2004: A 48-Year-Old Woman with Multiple Pigmented Lesions and a Personal and Family History of Melanoma, New England Journal Med pp. 350;9
71. Walterfang M, Wood SJ, Velakoulis D, Copolov D, Pantelis C.Diseases of white matter and schizophrenia-like psychosis.: Aust N Z J Psychiatry. 2005 Sep;39(9):746-56
72. Weinberg, R., Biology of Cancer, Garland (New York) 2007.
73. Winograd, T., F. Flores, Understanding Computers and Cognition, Addison Wesley (Reading, MA), 1987.
74. Wronski, M, Arbit, E. Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients. J Neurosurg 2000; 93:9.
75. Yu, C, Chen, JC, Apuzzo, ML, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. Int J Radiat Oncol Biol Phys 2002; 52:1277.
76. Zacest, AC, Besser, M, Stevens, G, et al. Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. J Neurosurg 2002; 96:552.

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