



# ADVANCES

A Monthly Update from the CEO

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## Fathers, Sons and Grandsons: New Genetic Testing for Prostate Cancer

### Overview

We try to give our children all that we can. Individually we give them half of their DNA. For our sons and grandsons, a greater susceptibility to prostate cancer can be inherited -- in the same way as eye color. Men are at an increased risk for prostate cancer if they have what human geneticists call an affected *first-degree relative*--a father, uncle, grandfather or brother with prostate cancer--on either side of the family. The more relatives a man has with a diagnosis of prostate cancer, the greater his lifetime risk of getting prostate cancer. Approximately 25 percent of all prostate cancer patients with the disease have a positive family history. In a recent large study of Scandinavian identical twins, hereditary factors explained 42 percent of the risk of developing prostate cancer.

Recently, several research papers have been published--notably a seminal one--in the *New England Journal of Medicine*. Partially supported by the PCF, it will have an impact on the sons and grandsons of men who are prostate cancer survivors.

PCF-supported scientists found that a combination of five gene variants called SNPs dramatically raises the lifetime risk of getting the disease in Swedish families. Added to family history, the five gene variants DNA test could account for 42 percent of all cases. The findings are important not just for the number of cases the DNA test might predict, but also because this relatively new approach — looking at combinations of genes, rather than focusing on a single gene is far more predictive. Complex diseases like prostate cancer and diabetes are increasingly being discovered to involve multiple genes or interactions rather than a single one in the 22,000 plus genes in the human genome.

The new SNP findings can have an important impact on where the PCF can make a difference in being the “lead investor” in prostate cancer *prevention and earlier microscopic detection* for our sons and grandsons. The purpose of this letter is to update you on the past four months of major research reports, and to inform you on what may lie on the horizon for genetic testing as a means of determining prostate cancer risk. To do that in context, I am providing some background on the founding of prostate cancer

genetics, now a booming research field, and my perspective on some of the field's "founding fathers". Finally, I will share some thoughts about what needs to start happening now in our clinical and research thinking if we are soon to predict our sons' and grandsons' risk for prostate cancer decades ahead of their 40<sup>th</sup> birthdays.

## **Founding the Field and "Founding Fathers" of Prostate Cancer Genetics**



Pat Walsh at Johns Hopkins started as a clinical scholar recording meticulous family histories as he saw patients for prostate cancer surgery. With this information he began building a data conducting analysis on extra blood samples. Walsh was the first to publish a paper on familial prostate cancer which opened the field in the late 1980s. The pioneering vision of this work cannot be overstated. Walsh began this work when less than 1 percent of the genes in the human genome that could link to prostate cancer were even identified. Today's biotechnology and computing capacity did not exist from the Human Genome Project. Further, there was only one laboratory in the world cloning DNA and studying genes in families with prostate cancer -- and it was in Baltimore. The occupant of that laboratory was Dr. William Isaacs who Walsh hired onto the faculty as a PhD scientist trained by Donald Coffey.

In the first year of the PCF (CaPCure), Isaacs and Walsh received significant PCF funding to expand the genetics effort, and share the data with others. Convinced more work in the area was essential beyond a single site in Baltimore, Mike Milken appeared on the Larry King Show. In that national appearance Milken used a 1-800 number and a personal appeal to recruit families with prostate cancer, nationally, for participating in research studies to move the field forward. The PCF's Competitive Awards funding in genetics for the first five years of the PCF strongly encouraged collaborations and international cooperation. That took hold. Within five years of founding of the PCF, there were eight centers working globally in consortium efforts on prostate cancer human genetics, and a field of study was established.

We just reviewed the international consortium efforts in prostate cancer human genetics at the Institute for Cancer Research in London that arose out of Baltimore and CaPCure. At this writing there are more than 50 centers in 30 countries participating in human prostate genetics collaborations.

It can be said that the PCF's stimulated research model "went global" first in human genetics. This type of research at a high level requires literally thousands of families and DNA samples. The datasets are most informative if thousands of patients and men in their families without prostate cancer from many centers are combined. To do the work that links family heredity to prostate cancer you also have compare that DNA analysis with cases of prostate cancer where there is not a family history. That early work in genetics needed new molecular tools to be developed. Creating the tools for the research --not just collecting the families and blood samples--was partly supported by the Milken Family Foundation, CaPCure Competitive Awards and David Koch-CaPCure directed awards at Johns Hopkins. Other groups at other centers followed suit in the late 1990s to

create large global clusters of families essential to understanding prostate cancer in different environments.

Several leading European and American prostate cancer geneticists were first trained at Johns Hopkins under the PCF's Competitive Awards. Many would then go on to be research directors at their own institutions by 2000 to "collect their own families." The "human capital" to conduct prostate cancer human genetics research in this century was also launched by the PCF towards the end of the last century. One exceptionally-gifted "young investigator" whose collaboration was supported in the Isaacs laboratory with PCF and David Koch-PCF directed awards, was a Fulbright Scholar from China, Jiangfeng Xu MD DsC. Dr. Xu and Dr. Isaacs began collaborating in 1995, and Xu is the leader of the research team that made its seminal report in the New England Journal. Xu is now professor and director of the Center for Human Genomics at Wake Forest University Cancer Center where a predictive test is now being developed for routine clinical use.

Koch-PCF funds were so substantial and flexible that they made testing and application of new SNP biotechnologies, software and equipment possible. This important Koch-PCF support is cited in the latest New England Journal Paper. In the late 1990s, NIH funding followed into the Human Genome Project and genetics projects. Soon other investigators in the US and Europe followed suit and began to receive funding for collecting DNA from families and studying genes that might be passed down as candidates for conferring prostate cancer.

The collection of family histories and DNAs, particularly in families in which the disease was diagnosed before the age of 60 years, led studies that identified several genes out of the 22,000 in the human genome that may be involved in rare cases of hereditary prostate cancer. One of these, *HPCI*, codes for RNase-L protein gene and is important because it suggests that prostate cancer could arise from "hit and run" asymptomatic bacterial or viral infections in a young man's prostate. Rather than prostate cancer being caused by one particular virus, it may be that any type of inflammation from microbes can fuel prostate cancer if a man carries particular variant genes. Currently, the PCF is funding work aimed at identifying as yet unidentified viruses (pathogens) and reducing the cancer-causing inflammatory biochemistry. It is a new area for nutritional research we were not concentrating on until the RNase-L gene was found.

Consistent with the global nature of these efforts, the latest New England Journal study had 21 authors drawn from the US and Sweden and was led by Jianfeng Xu at Wake Forest University in Winston-Salem, NC, and involved Johns Hopkins University in Baltimore, the Karolinska Institute in Stockholm, TGen in Phoenix, and the Harvard School of Public Health. It involved 2,893 men with prostate cancer and 1,781 similar men who did not have the disease.

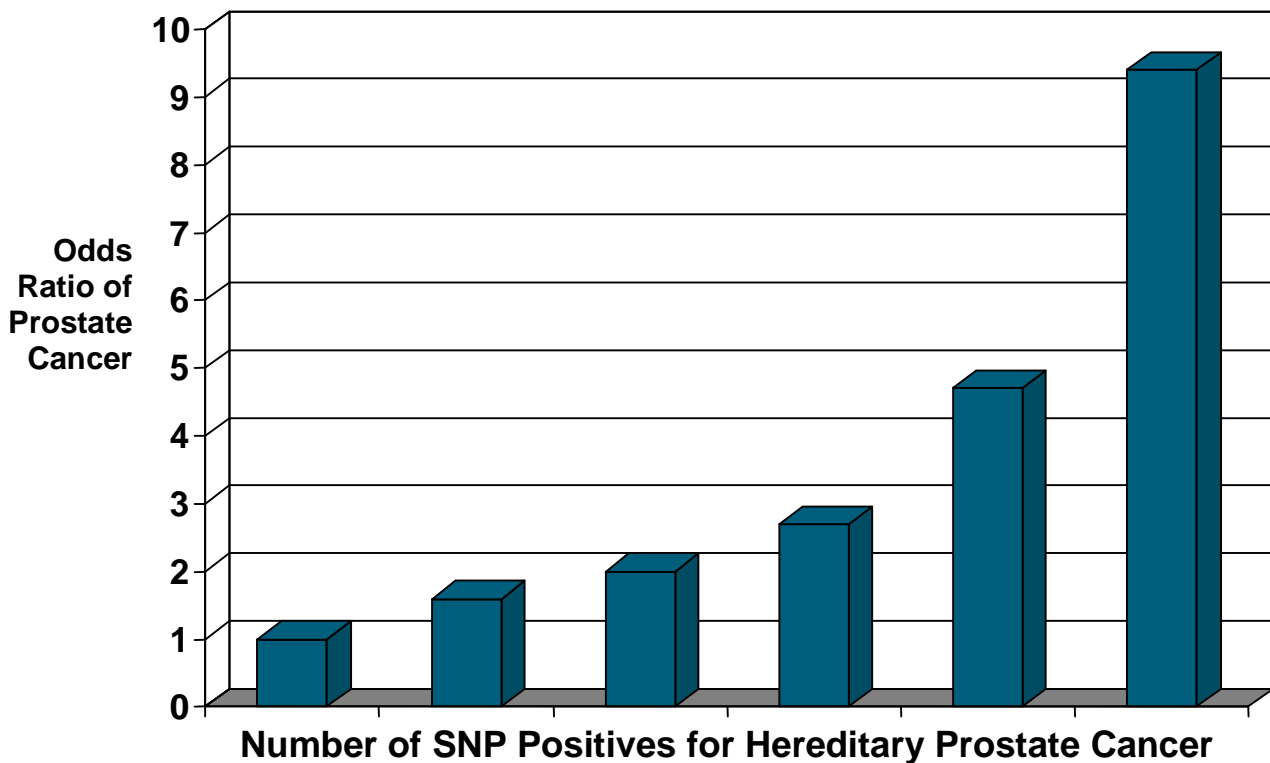
Sweden is an excellent study environment because computerized records there are excellent, DNA had been collected, and the population is so ethnically similar and well-suited to gene studies. The study population was composed of Swedish men in whom prostate cancer was diagnosed between 2001 and 2003. Researchers looked for "hot spots" of differences in genes of the men with cancer compared to the others, then

focused on the five most common variants, which were single letter changes in the gene's usual DNA alphabet. The variants are "SNPs". When four or five variants were present, men were more than *four times more likely* to develop prostate cancer than those with none of the markers. When family history was added in, men with five of the six factors were *more than nine times more likely* to develop the disease. These six factors accounted for 46 percent of the prostate cancer cases in the study.

***"Fortunately, a ten-fold risk for developing prostate cancer does not appear common. It was found in only 1.4 percent (40 of the 2893) prostate cancer subjects in the study."***

The diagnostic five SNPs lie in the DNA code within our 23 chromosomes: two SNP markers are on the "long arm" of chromosome 8, and three SNPs are on the "long arm" of chromosome 17. Five SNPs do not tell the whole story, however. When a positive family history was added to the analysis as a sixth high-risk variable (the five SNPs plus family history), the risk ratio for prostate cancer was 9.46. In other words, with a family history and five "positive" SNP DNA markers, the risk of prostate cancer was about ten times that of the regular Scandinavian population. This is the highest risk ratio for prostate cancer ever reported in prostate cancer as a clinical test. Fortunately, a ten-

fold risk for developing prostate cancer does not appear common. It was found in only 1.4 percent (40 of the 2893) prostate cancer subjects in the study. For a man without a family history of prostate cancer a test with four or five of the high-risk DNA markers would increase the lifetime risk of prostate cancer by a factor of about 4.5.



## Limitations of the Current Work and Implications for Families

There are limitations in this work. Genetic tests are unlikely to alter the screening behavior of men who are already under surveillance for prostate cancer by the monitoring of prostate-specific antigen (PSA). Most men with a family history of prostate cancer are aware that screening is recommended as early as the age of 40 without a DNA test. In addition, according to Dr. Ros Eeles at the Institute for Cancer Research in London, perhaps only 50 percent of the genome's SNPs have been looked at for genetic testing of prostate cancer. It is likely that the test will be improved in the coming years, likely with the addition of data from European centers.

In other words, the new genetic risk test will not replace annual digital rectal examination and PSA screening. The SNP test gives odds in a lifetime of developing prostate cancer, not where it is, or if it is there yet. Before recommendations can be made to screen all men by "genotyping them" for the five SNPs on chromosomes 8 and 17, it is important to prove the findings extend beyond Swedish men. Such an analysis could be carried out with the use of stored DNA samples from US randomized trials, such as the Prostate Cancer Prevention Trial and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Both trials collected baseline DNA samples from healthy men who were followed for the development of prostate cancer, and both have information on biopsy results and a Gleason grade. We just reviewed plans at the Institute for Cancer Research in the United Kingdom to do these types of studies in Britain and the European Union.

Another problem could be over diagnosis and "false positives" in the genetic testing. Most experts believe that prostate-cancer screening has resulted in a substantial degree of over-diagnosis of some low grade cancers that never would have presented clinically as well as allowed detection of cancers that, left untreated, would be lethal. For this reason, there is a need for markers that can distinguish between aggressive and indolent cancers. The PCF is already funding work on biomarkers of potentially lethal cancers with the EPCA2 test, and Chromosomal ERG-ETV Fusions tests in the urine at this time.

An additional limitation of the SNP DNA test is that it does not define the type of prostate cancer that might emerge in a lifetime. The new Wake Forest SNP DNA test does not distinguish between Gleason Grade. In fact, in the *New England Journal* paper the test could not predict Gleason Grade or aggressive versus less aggressive tumors. Unfortunately, the Wake Forest markers do not help urologists determine which cancers need treatment and which do not. Furthermore, the SNP tests did not correlate with levels of PSA. An intensification effort is needed in research for non-invasive ways to "image" very early prostate cancer lesions in men in their 30s who have 5+ SNP tests. None of the current imaging modalities, MRI, CT Scan, ultrasound, or nuclear medicine scans can detect prostate cancer lesions the size of the period at the end of this sentence. The limits of all our imaging technologies were just reviewed two weeks ago at a special conference hosted by the National Cancer Institute at which over 20 PCF research awardees were in attendance. PSA and PSA velocity after age 40, while useful, will need to be replaced with ultra-sensitive assays for young men in their 20s and 30s. In this respect the new SNP DNA test is more like a screening cholesterol and lipid profile.

Those blood tests do not predict the severity of the heart attack or stroke, only its higher likelihood so that lifestyle changes and medications like statins can be employed.

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We do not yet have a proven “statin” for prostate cancer lifetime risk reduction. So the work there begins in earnest as the SNP test is validated and refined. It is likely dietary modifications that reduce reactive oxygen exposure in the prostate through diet and exercise are a rational approach. For example, anti-oxidant polyphenols in pomegranate juice, or other dietary supplements taken in the first, second third and fourth decades of a man’s life could potentially reduce the “initiation” of cancers. The PCF is funding “nutritional prevention” experiments in genetically engineered mice that are genetically programmed to get prostate cancer. At the 2008 Scientific Retreat this fall, the PCF is going to create a research task force to begin defining the clinical research agenda for nutritional sciences and chemoprevention clinical trials for the perhaps two percent of

young men in their twenties who have genetically a ten times increased lifetime risk of prostate cancer.

Chemoprevention agents for prostate cancer would be rationally tested in young men with SNP+ tests and a lifetime elevated risk of ten times that of the normal population. One of these agents is Finasteride. The drug, recently featured in the *New York Times*, does have side effects. However, it may reduce initiation of some low grade prostate cancers. It is likely it will be used in clinical trials in men in their 20s or 30s who have 5+ SNP DNA tests, and a positive family history to test for lifetime reduction of prostate cancer. The use of Finasteride needs always to be discussed with a urologist prior to initiating treatment.

On May 21, 2008, President George W. Bush signed the Genetic Information Nondiscrimination Act (GINA). At last, the United States has a federal law that protects consumers from discrimination by health insurers and employers on the basis of genetic information. With this type of discrimination a now being a criminal offense, the road is now clear for more genetic testing and genetic counseling to occur. What follows is information from the New England Journal of Medicine on the new GINA law.

## Quick Guide to the U.S. Genetic Information Nondiscrimination Act

Source: *New England Journal of Medicine* - 06/19/2008

### What GINA Does

Prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums

Prohibits an insurer from requesting or requiring that a person undergo a genetic test

Prohibits employers from using a person's genetic information in making employment decisions such as hiring, firing, job assignments, or any other terms of employment

Prohibits employers from requesting, requiring, or purchasing genetic information about persons or their family members

Will be enforced by the Department of Health and Human Services, the Department of Labor, and the Department of Treasury, along with Equal Opportunity Employment Commission; remedies for violations include corrective action and monetary penalties

### What GINA Does Not Do

Does not prevent health care providers from recommending genetic tests to their patients

Does not mandate coverage for any particular test or treatment

Does not prohibit medical underwriting based on current health status

Does not cover life, disability, or long-term-care insurance

Does not apply to members of the military

### Key Terms

"Genetic information" includes information about: a person's genetic tests; genetic tests of a person's family members (up to and including fourth-degree relatives), any manifestation of a disease or disorder in a family member; participation of a person or family member in research that includes genetic testing, counseling or education

"Genetic tests" refers to tests that assess genotypes, mutations or chromosomal changes

Routine tests such as complete blood counts, cholesterol tests, and liver-function tests are not protected under GINA.

Genetic testing without the involvement of an established genetic counselor at a major academic center should be avoided. According to Dr. Xianfeng Xu the SNP genetic test for prostate cancer will be available beginning Q2 2009. More information can be found at Wake Forest Universities CLIA (Clinical Laboratory Improvement Amendments)-

certified laboratory at Wake Forest University School of Medicine. For more information, visit the website [www.ProactiveGenomics.com](http://www.ProactiveGenomics.com); telephone 866-487-2344.

The U.S. Surgeon General and other federal health agencies have recently launched the U.S. Surgeon General's Family History Initiative to encourage people to learn more about their family health history. A web site for the project gives families an internet tool for advice on how to track this information at <http://www.hhs.gov/familyhistory>. You might want to load your own data.

## **Summary**

Exploration of all our genes will change global health, the economy, and perhaps our society as we learn we are all genetically at risk for chronic and acute diseases as a part of our DNA's life endowment. All that is described above was made possible by 1) inquisitive, scholarly doctors talking to patients about genetics, 2) a new cadre of PhD and MD PhD geneticists funded by the PCF starting in 1994, 3) recruitment of "prostate cancer" families to genetic studies by increasing awareness for them (as exemplified by Mike Milken's appearance on the Larry King Show), 4) DNA biotechnologies analyzing saliva or a teaspoon of blood at speeds inconceivable five years ago.

As new recommendations and guidelines are developed, we will post them on our website: [www.pcf.org](http://www.pcf.org). For our sons and grandsons, an intensification of research on dietary and perhaps low risk pharmacologic interventions accompanied with earlier cancer detection technologies is imperative. At the PCF we are very engaged with the NCI and Department Defense in launching new research efforts in these areas.

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