Age, Sex Sterioids, Inflammation and Prostate DNA Methylation.

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I would like to take this opportunity to thank the PR-AABRE organizers; Drs Maria Miranda, Ida Mejais and Mr. Guillermo Diaz for inviting me to your beautiful country and also giving me the opportunity to present my work studying the molecular events involved in prostate cancer with particular emphasis to understand the disease etiology and or progression.

bkwabi-addo, 2/4/2008

*Age-adjusted to the 2000 US standard population.
the trend of cancer incidence among US men. This is all age-adjusted incidence expressed per 100,000 of US male population. The data shows a rapid increase in cancer incidence between 1988 to 1993 presumably due to increased detection by PSA.

Bkwabi-Addo, 2/12/2008
Prostate Cancer is now the most common non-skin cancer diagnosed and the 2\textsuperscript{nd} cause of deaths due to cancer in men in most western countries.

- **Age**
- **Family history**
- **Ethnicity**

Other risk factors:

- Exposure to both endogenous and exogenous factors - androgens and vitamin D
- Sexually transmitted diseases/Prostatitis/chronic inflammation/Obesity
- Smoking/Alcohol
- BPH
As we all know, prostate cancer is now a commonly diagnosed disease among men and is the second cause of deaths due to cancer in men in most western countries. Despite the many studies that have been carried out, not all the etiological factors have yet been clearly identified. Aging, family history and geographic origin or ethnicity are the only well-established risk factors for the disease. Other risk factors including exposure to both endogenous and exogenous factors such as sex steroid hormones, vitamin D, sexually transmitted diseases, chronic inflammation, obesity, smoking, alcohol abuse, diabetes, BPH have all been investigated but their roles in prostate cancer etiology remains unclear.

bkwabi-addo, 2/4/2008
African American men are at increased risk for both diagnosis of PCa (1.6x) and death from PCa (2x). Why the disparity?

Environmental
SES
Genetic
So AA men are at increased risk for prostate cancer over caucasians (1.6x) and deaths from pca 2-fold over caucasians due to environmental, genetic and also socio-economic status.
Molecular Genetics of PCa

- **Germline**
  - Inherited susceptibility
    - Familial vs non-familial
      - Rare, high penetrance genes vs common low penetrance gene
      - Genome wide association studies
  - DNA rearrangements, Copy number changes

- **Somatic**
  - Mutation
    - TCGA project
  - Gene expression Profiling
  - Epigenetic
    - hypermethylation
the genetics of pca has proven difficult to study. studies in twins that compare the concordant occurrence of pca in monozygotic twins with that in dizygotic twins have consistently revealed a stronger hereditary component in the risk of pca than in any other type of cancer in humans. reports suggest that men with pca were more likely than their spouses to report having an affected brother or father and estimated that the presence of one, two, or three affected family members increased the risk of pca in 1st-degree relatives by a factor of 2, 5, and 11 respectively whereas the risk in a more distant relative was only marginally increased. at the time of diagnosis, prostate cancer cells contain many somatic mutations, gene deletions, gene amplifications, chromosomal rearrangements and changes in dna methylation. these alterations probably accumulate over a period of several decades. the most commonly reported chromosomal abnormalities appear to be gains at 7p, 7q, 8q, and xq, and losses at 8p, 10q, 13q and 16q.
## Germline variations and somatic genome alterations in prostate cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Alteration</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RNASEL</strong></td>
<td>1q24–25</td>
<td>Germline; base substitutions/deletions</td>
<td>Encodes interferon-inducible endoribonuclease involved in RNA degradation</td>
</tr>
<tr>
<td><strong>ELAC2</strong></td>
<td>17p11</td>
<td>Germline; base insertions/substitutions</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>MSR1</strong></td>
<td>8p22</td>
<td>Germline; base substitutions</td>
<td>Encodes subunits of class A macrophage scavenger receptor</td>
</tr>
<tr>
<td><strong>AR</strong></td>
<td>Xq11–12</td>
<td>Germline; polymorphic trinucleotide repeats</td>
<td>Encodes androgen receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somatic; amplification and mutations</td>
<td></td>
</tr>
<tr>
<td><strong>CYP17</strong></td>
<td>10q24.3</td>
<td>Germline; base substitution in promoter</td>
<td>Encodes enzyme cytochrome P-450c17</td>
</tr>
<tr>
<td><strong>SRD5A2</strong></td>
<td>2p23</td>
<td>Germline; base substitutions</td>
<td>Encodes 5α reductase type 2</td>
</tr>
<tr>
<td><strong>GSTP1</strong></td>
<td>11q13</td>
<td>Somatic; CpG island hypermethylation</td>
<td>Encodes carcinogen detoxification enzyme</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NKX3.1</strong></td>
<td>8p21</td>
<td>Somatic; allelic loss</td>
<td>Encodes prostate-specific homeobox gene</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>10q23.31</td>
<td>Somatic; allelic loss, mutations, probable CpG island hypermethylation</td>
<td>Encodes phosphatase active against protein and lipid substrates</td>
</tr>
<tr>
<td><strong>CDKN1B</strong></td>
<td>12p12–13</td>
<td>Somatic; allelic loss</td>
<td>Encodes p27, cyclin-dependent kinase inhibitor</td>
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</table>
Pca is associated with the greatest heritable risk of any human cancer. However, unlike the relatively common somatic genetic alterations observed in colon cancer such as p53 and K-ras mutations, the molecular genetics underlying this disease displays a great deal of heterogeneity both between individuals as well as within an affected organ. The diversity of currently identified somatic genetic abnormalities associated with pca suggests that there is not a single dominant molecular pathway required for prostate carcinogenesis.

To date, numerous germline pca susceptibility genes as well as somatic genome alterations (mutations, deletions, rearrangement, amplifications and DNA methylation have been identified) as shown here.

RNASEL: Changes in the activity of the proteins encoded by genes involved in the innate immune response may result in an inadequate ability to fight infection leading to chronic inflammation. The RNASEL gene encodes a widely expressed latent endoribonuclease that is involved in interferon-inducible RNA degradation. Once activated by interferon, cells containing a functional RNASEL gene produce an enzyme that degrades single stranded RNA, leading to apoptosis. This pathway is thought to be one method that cells utilize to combat viral infection. Mice bearing a homozygous deletion in the RNaseL gene display diminished anti-viral activity in response to interferon-alpha. Interestingly the RNASEL has been linked to the familial prostate cancer locus HPC1 on chromosome 1. Mutations in the RNASEL gene have been linked to familial prostate cancer in Finnish as well as Ashkenazi Jewish men. It is likely that genetic variant in RNASEL increases the risk for PCA only in the presence of some environmental exposure (e.g., viral infection) that may vary from study population to population.

MSR1 - another component of the innate immune response is the macrophage scavenger receptor (MSR) 1, a macrophage plasma membrane spanning protein that is capable of binding to a variety of ligands, including bacterial lipopolysaccharide and lipoteichoic acid, as well as oxidized HDL and LDL. The msr1 gene is located on chr 8p22 an area of frequent allelic loss in PCA. mice deficient in MSR are highly susceptible to infection by Listeria monocytogenes, E. coli. Several germine mutations have been observed in some families with hereditary PCA. Areas within the prostate that shows evidence of inflammation are often populated by macrophages that express MSR1.

PCA is usually treated with androgen suppression, antiandrogens, or a combination of the two. Despite an initial response, progression is inevitable, because of the emergence of androgen-independent prostate cancer cells. In most androgen-independent PCs, expression of the receptor and many aspects of its function are maintained. There is evidence that receptors drive the proliferation of androgen-independent PCA cells even in the absence of androgens. Many somatic alterations of AR have been detected in PCA, especially in those that progress despite hormonal treatment. AR amplification, accompanied by overexpression of AR, may promote the growth of androgen-independent PCA cells by increasing the sensitivity of PCA cells to low levels of circulating androgens. In many AR mutations, the ligand specificity of the receptor can be altered, permitting activation by nonandrogens or even by antiandrogens. In the absence of AR mutations, androgen-independent PCA may progress through the activation of ligand-independent androgen receptor signaling pathways.

cyp17 encodes cytochrome p-450c17alpha, an enzyme that catalyzes key reactions in sex steriod biosynthesisbase substitution in transcriptional promoter (T to C transition leads to new Sp1 recognition site). Linkage data suggest that another variant CYP17 allele is associated with prostate cancer.

srd5a2; encodes the predominant isomzime of 5-alpha-reductase in the prostate, an enzyme that converts testosterone to the more...
potent dihydrotestosterone. 2 common polymorphic variant SRD5A2 alleles have been described. The alleles that encode enzymes with increased activity have been associated with an increased risk of pca and with a poor prognosis for men with pca. In addition to AR, CYP17 and SRD5A2, polymorphic variants of a number of other genes have been proposed as possible contributors to the risk of pca.

b12  
nkx3.1, located at 8p21, encodes a prostate-specific homeobox gene that is essential for normal prostate development. nkx3.1 has been noted to bind DNA and repress psa gene transcription. heterozygous or homozygous deletion of nkx3.1 in mice leads to prostate displasia and lesions resembling PIN. In men loss of heterozygosity at polymorphic 8p21 sequences has been noted in as many as 63% of PIN lesions and 90% of prostate cancers. Despite allelic loss in this region, somatic mutations of NKX3.1 have yet to be identified in a single case of pca, hence calling into question the role of nkx3.1 inactivation in pca development. Nevertheless, loss of nkx3.1 expression in pca tissue has been reported to be associated with disease progression. as nkx3.1 plays an important role in prostate development, one might speculate that chronic inflammatory injury might potentiate abnormal prostate gland regeneration in the setting of absent or diminished nkx3.1 activity. the relationship between somatic nkx3.1 genomic alterations and reduced knx3.1 expression in the context of pca is yet to be determined.

b13  
the pii class glutathione s-transferase (GSTP1) gene encodes an enzyme that acts as a carcinogen detoxifer. GSTP1 actively protects the cell from oxidative genome damage mediated by carcinogens and electrophilic compounds. cells devoid of gstp1 accumulate oxidized DNA bases in response to oxidative stress, a situation that may occur at sites of inflammation. mice homozygous for gstp1 display a strong tendency to develop skin papillomas at a frequency significantly higher than control animals. hypermethylation of cpg island sequences in the promoter region of gstp1, a somatic genome alteration, is an exceedingly common early epigenetic event in pca, occurring in >90% of cases.

b14  
pten, the gene for phosphatase and tensin homologue, a tumor suppressor gene encoding a phosphatase active against both proteins and lipid substrates, is a common target of somatic alteration during prostate cancer progression. cdkn1b; reduced levels of p27, a cyclin-dependent kinase inhibitor encoded by the cdkn1b gene, also are common in pca, particularly in pca with a poor prognosis.
# Sequence variation, ethnicity and prostate cancer susceptibility

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>African American</th>
<th>European-American</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochromes p450 CYP3A</td>
<td>CYP3A4*1B</td>
<td>59%</td>
<td>8%</td>
<td>Increased risk of PCa with family history</td>
<td>Zeigler-Johnson et al., 2008</td>
</tr>
<tr>
<td></td>
<td>CYP3A4*3</td>
<td>35%</td>
<td>4%</td>
<td></td>
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</tr>
<tr>
<td>Vitamin D Receptor</td>
<td>5132 C/T</td>
<td>OR = 1.83</td>
<td>OR = 1.10</td>
<td>Increased susceptibility to PCa</td>
<td>Kidd et al., 2005; Oakley-Girvan et al., 2004</td>
</tr>
<tr>
<td></td>
<td>4266 G/A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Androgen Receptor</td>
<td>CAG/ GGN repeats</td>
<td>Short repeats</td>
<td>Long repeats</td>
<td>Inverse association between # of repeats and risk to PCa</td>
<td>Ingles et al., 1997; Hakimi et al., 1997; Cude et al., 2002</td>
</tr>
<tr>
<td>Steroid 5a-reductase SRD5A2</td>
<td>V89L (L allele)</td>
<td>27%</td>
<td>30%</td>
<td>Decrease conversion of testosterone to DHT</td>
<td>Zeigler-Johnson et al., 2002</td>
</tr>
</tbody>
</table>
there are significant differences in the frequency of putative pca risk genotypes. Africans and AA are more likely than Caucasians, latinos and asians to have genotypes at some of these genes that have been associated with increased risk of pca or poorer clinical prognosis. overall agreement among these findings suggests that african popns may be at genotyping high pca risk. Genotypic susceptibility represents only one piece of the complex nature of the prostate cancer etiology. underlying differences in susceptibility to develop pca is manifest through exposure to environmental agents, social environmental and neighborhood context, behavior, access to quality healthcare, and other factors.

bkwabi-addo, 6/25/2008
8q24 PCa loci confirmation studies

- Severi et al. Australian
- Yeager et al. PLCO (CGEMS)
  Nat Genet. 2007 Apr 1
- Haiman et al. EA, JA, AA, Lat, HI
  Nat Genet. 2007 Apr 1
- Gudmundsson et al. Icelandic, EA, AA
  Nat Genet. 2007 Apr 1
- Wang L et al. EA (Mayo Clinic)
  Cancer Res. 2007 Apr 1
- Schumacher FR BPC3 Cancer Res. 2007 Apr 1
- Suuriniemi et al. EA

Most important finding in PCa genetics to date!!!
DNA methylation changes during prostate cancer initiation and progression

The most common alteration at the DNA level in prostate cancer is an epigenetic change occurring in the earliest steps in cancer initiation.

Yegnasubramanian et al., 2007
For the next part of my presentation, I am going to switch my talk from looking at the role of genetics to epigenetic abnormalities in understanding their relative contribution to prostate cancer etiology and/or progression.

The most common alteration at the DNA level in prostate cancers is an epigenetic change.

bkwabi-addo, 2/7/2008
DNA methylation occurs at CpG dinucleotides in mammalian genomes

**de novo methylation**

5’…ACGT…3’
3’…TGCA…5’

5-me

5’…ACGT…3’
3’…TGCA…5’

5-me

5’…ACGT…3’
3’…TGCA…5’

**maintenance methylation**

[Diagram showing the process of DNA methylation, including the role of S-adenosylmethionine, 5-methylcytosine, DNA methyltransferase, and demethylase.]
DNA methylation is a covalent modification process whereby methyl donors from S-adenosyl-methionine is covently added to the cytosine ring to form methyl cytosine. This process is catalysed by enzymes called DNA methyltransferases (DNMTs). In humans and other mammals, this modification is imposed only on cytosines that precede a guanosine in the DNA sequence (CpG dinucleotide).

The overall frequency of CpGs in the genome is substantially less than what would be mathematically predicted, probably because DNA methylation has progressively depleted the genome of CpG dinucleotides over the course of time. The mechanism of the depletion is related to the propensity of methylated cytosine to deaminate, thereby forming thymidine. If this mutation is not repaired, a cytosine-to-thymidine change remains. The depletion of CpG dinucleotides in the genome corresponds directly to sites of such nucleotide transitions, and this change is the most common type of genetic polymorphism (variation) in human populations.

DNA methylation is established by de novo methyltransferases. Replication of homomethylated DNA produces hemimethylated DNA in which one strand of the DNA remains methylated and the newly synthesized is unmethylated. Hemimethylated DNA can become homomethylated by maintenance methyltransferases which place a methyl group at the 5'-CG-3' complimentary to a methylated 5'CG-3.
DNA methylation can lead to silencing of gene expression

Robertson and Wolffe, Nat Rev Genet, 2000
It is well established that DNA methylation is involved in regulating gene transcription. This can occur by a variety of mechanisms. The interactions of several transcription factors whose binding sites contain CpG dinucleotides has been shown to be methylation-sensitive. However, methylated DNA more profoundly affects transcription by interacting with methyl-CpG-binding proteins and associated factors that alter chromatin structure.

How proteins with methyl-CpG-binding activities repress transcription is under active study. There is evidence for a variety of complex mechanisms. One key mechanism involves MBD-mediated recruitment to methylated DNA one of two co-repressor complexes, sin3 and mi-2/nurD, which in turn recruit a core histone deactylase complex consisting of HDAC1, HDAC2 and two Rb associated histone binding proteins. Additional co-repressors complex exists, however, their role in silencing mechanisms that involve DNA methylation has not been demonstrated. HDACs remove acetyl groups from the lysine residues found at the N-termin of histone H3 and H4. Their removal results in an increase in the positive charge of the histone which is hypothesised to condense chromatin by enabling a tighter association between the histones and the negatively charged DNA. This may in turn silence transcription by limiting transcription factor binding. This description is clearly over-simplification.
Proposed methylation patterns in normal and cancer genomes

Herman and Baylin, NEJM, 2003
in most of the mammalian genome, which is depicted here as exons 1, 2, and 3 of a sample gene introns of the gene and regions outside the gene, the CpG dinucleotide has been depeted during evolution as shown by the small number of such sites (circles). small regions of dna, approximately 0.5 to 4.0 kb in size, harbour the expected number of CpG sites and are termed CpG islands. Most of these are associated with promoter regions of approximately half the genes in the genome (numerous circles surrounding and within exon 1 of the sample gene). In normal cells, most CpG sits outside of CpG islands are methylated (black circles) whereas most CpG-island site js in gene promoters are unmethylated (white circles). This methylated state in the bulk of the genome may help suppress unwanted transcription, whereas the unmethylated state state of the CpG islands in gene promoters permit active gene transcription (arrow in upper panel). In cancer cells, the DNA-methylation and chromatin patterns are shifted. Many CpG sites in the bulk of the genome and in coding regions of genes, which should be methylated, become unmethylated and a growing list of genes have been identified as having abnormal methylation of promoters containing CpG islands, with associated transcriptional silencing (red X at the transcription start site). Although there are possible explanations and findings from ongoing investigations, it is not known why the DNA-methylation enzymes fail to mthylate where they normally would and which of these enzymes are mediating the abnormal methylation of CpG islands in promoters.

bkwabi-addo, 2/7/2008
Diverse cell and tissue damaging stresses accumulate over time in the prostate

De Marzo et al., 2007
underlying these aberrant DNA methylation changes is the accumulating body of data hinting that normal prostate cells may be subjected to a relentless barrage of genome-damaging stresses due to both exogenous and endogenous carcinogens, with damage accumulating over time. Thus a better understanding of the causes of how these factors affect methylation would shed some light on the pathophysiology of CGI methylation events in PCA and other human cancers.

bkwabi-addo, 6/26/2008
De novo DNA methylation changes in prostate cancer

• Age

• Carcinogen or Sex Steroid hormone exposure

• Chronic or recurrent inflammation
DNA methylation changes, aging and the human prostate

Kwabi-Addo et al., 2007
for each cpg island studied, the percentage of methylation at a specific promoter was expressed as a function of age. there was considerable variation in the % of cpg island methylation in the individual patient sample studied presumably reflecting random variability in tissue composition and variable methylation level per cell. the variable range of methylation could also reflect differences in genetic susceptibility to methylation, lifestyle or exposure factors (including diet) and the random nature of the methylation event.

we observed a significant increase in promoter methylation with age for several cpg islands including gstp1, rassf1a, nko2-5, rarbeta2 and esr1. however, the myod1, ar and cistn1 and p16 did not show methylation as a function of age in normal human prostate tissues suggesting that not all genes show age related dna methylation in the human prostate and clearly with some genes such as myod1 and po16 that shows such phenomenon in other tissues such as the colon there is tissue specificity.
DNA methylation changes and aging and the human prostate

Kwabi-Addo et al., 2007
An unbiased analysis of all the data by z-score normalization for the 9 genes showed a strong correlation with age in the normal prostate tissues. These results indicate that DNA methylation increases with age in the normal human prostate.
Comparison of DNA methylation level between normal and prostate cancer tissues

Kwabi-Addo et al., 2007
the use of DNA methylated genes as diagnostic biomarkers has potential application for distinguishing between normal and PCA tissues and for identifying premalignant state. An ideal biomarker would have low levels of methylation in the normal tissue and be highly elevated in the cancer and premalignant state. We wanted to identify novel biomarkers comparable to GSTP1 as non-invasive diagnostic tools for identifying premalignant prostate disease. To achieve this we compared the level of the methylation in normal and PCA tissues from 3 different sources, namely normal prostate tissues from organ donors, cystoprostatectomy for bladder cancer patients and matched benign and prostate cancer tissues from cancer patients. As compared with the normal prostate tissues we observed more extensive methylation in PCA tissues. For RARB2 gene the average methylation seen in cancer samples was at least 2.7 fold higher when compared to the normal prostate tissues but there was no significant difference between the normal prostate tissue from different sources. Similarly for the RASSF1A gene, the average methylation level in PCA tissues was at least 2 fold higher compared to that in normal prostate tissues. Furthermore, the methylation in the benign tissues from cancer patients was significantly higher when compared to the normal prostate tissues from organ donors and the cystoprostatectomy for bladder cancer patients. Because RASSF1A methylation levels is low in normal prostate tissues and elevated in the PCA and surrounding benign tissues, quantitation of RASSF1A CpG island could also be useful for distinguishing between normal and PCA. GSTP1 methylation is at least 5 fold higher in cancer samples compared to normal tissues from organ donors and benign prostate tissues from cancer patients. However, the methylation level in the cancer samples was only 1.5 fold higher compared to that of the normal tissues from cystoprostatectomy for bladder cancer patients. This result can be explained by the high methylation levels observed in normal aging prostate tissues. The average methylation of NKX2-5 was about 3 fold higher than in normal samples, however the methylation levels were virtually identical among the 3 different sources of normal prostate tissues analyzed suggesting NKX2-5 methylation could also be a good candidate for distinguishing between normal and prostate cancer tissues. Overall ESR1 and CLSTN1 methylation levels were lower however the methylation level was approximately 2 fold higher in cancer compared to normal. Our primary data suggests that NKX2-5 could be a potential biomarker that could be useful for distinguishing between normal and prostate cancer tissues.

bkwabi-addo, 2/8/2008
Identification of differentially hypermethylated genes in human prostate cancer cell line, LNCaP

Kwabi-Addo et al., 2008
to identify novel cpg islands that are aberrantly methylated in pca, we used methylated cpg island amplification (MCA) coupled with promoter cpg microarray analysis. results demonstrate several genes to be differentially hypomethylated or hypermethylated in pca. while genome-wide hypomethylation which could lead to activation of previously silenced genes is seen in some advanced metastatic pca, most studies have emphasized dna hypermethylation as an important mechnsim for inactivation of key regulatory genes in pca.

bkwabi-addo, 2/8/2008
Methylation ratio in cancer cell lines of MCA-RDA genes

Chung, Kwabi-Addo et al., 2008
we have identified several novel genes in our microarray analysis that shows differential methylation level in cancer cells and tissues compared to benign tissues from different origins.

bkwabi-addo, 2/8/2008
On going studies

Carry out genome wide analysis on specimens from epidemiological cohorts to identify novel prognostic and predictive DNA methylation biomarkers

Validate these biomarkers in large epidemiological cohorts

Much is left to be learned

Causal variation among individual

Gene X environmental interaction

Strong combined effect on PCa risk and have utility in predicting individual PCa risk?

Do these variation account for disparities in incidence among different groups?
## Acknowledgements

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<tr>
<th>The Human Genome Center at Howard University</th>
<th>Johns Hopkins Medical Institute</th>
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<tr>
<td>Georgia M. Dunston</td>
<td>William G. Nelson</td>
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<td>Srinivasan Yegnasubramanian</td>
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<td>Michael Ittmann</td>
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[http://cancer.howard.edu](http://cancer.howard.edu)