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TITLE: "Integrated Genomic Biomarkers to Identify Aggressive Disease in African Americans with Prostate Cancer"

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of our research is to identify somatic copy number alterations and methylation markers in the primary tumors of African American (AA) men that can serve as a component of their recurrence risk assessment and be applied in treatment planning in attempt to reduce the racially disparate rates of mortality from prostate cancer. Through whole genome copy number alteration and methylation scans, the study will identify individual and integrated DNA-based biomarkers of biochemical recurrence in 200 AA men (100 with and 100 without biochemical recurrence). These biomarkers will then be validated in an independent set of 200 AA men. In the first year of funding, we have enumerated both discovery and validation samples; have obtained formalin fixed paraffin embedded blocks from 300 of these men; have completed pathology review of the complete discovery sample tumors; macrodissected and performed DNA extraction from 141 tumors; completed the running and quality control of 60 tumors on the copy number assay; completed the running and quality control of 48 tumors on the Illumina EPIC methylation microarrays. From the resulting copy number and methylation data, we have preliminary results for Aim 1 suggesting the utility of using the GEMCaP for prediction of biochemical recurrence in AA men, and further encouraging findings that suggest many, but not all, previously identified CpG methylation sites associated with biochemical recurrence in European American men are also associated with risk of recurrence in AA men. In addition, we also present finding from The Cancer Genome Atlas on copy number alterations that differ by race-ethnicity in AA vs. EA men with prostate cancer and are consistent with race-ethnicity differences observed in breast cancer. We intend to test these cross tumor site race-differentiated copy number alterations with biochemical recurrence in our study following completion of the discovery cohort. We are also expand the sample size for our manuscript exploring the effectiveness of a commonly used clinicopathologic predictor of prostate cancer in AA men and whether that effectiveness depends on genetic African ancestry, which is significant as we proposed that our genomic biomarkers would add to this established predictor.

15. SUBJECT TERMS

prostate cancer; DNA; copy number alterations; methylation; biomarker; racial disparities; integrative.

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1. INTRODUCTION:

Approximately ~33,000 men die each year from prostate cancer (CaP), in particular from disease recurrence. African American men have higher CaP mortality rates than age matched European American males. Risk of disease recurrence after primary treatment is difficult to predict with clinical variables and prostate specific antigen. Robust methods for risk stratification of prostate tumors are needed to enable men and their physicians to safely select between post-treatment surveillance and immediate adjuvant therapy. The purpose of our research is to use a mulit-omic approach to identify somatic copy number alterations and methylation markers in the primary tumors of African American men that can serve as a component of their recurrence risk assessment and be applied in treatment planning to help reduce the racially disparate rates of mortality from CaP. Through whole genome copy number alteration and methylation scans, the study will identify individual and integrated DNA-based biomarkers of biochemical recurrence in 200 African American men (100 with and 100 without biochemical recurrence). These biomarkers will then be validated in an independent set of 200 African American men.

2. KEYWORDS:

prostate cancer; DNA; copy number alterations; methylation; biomarker; racial disparities; integrative.

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Major Task #1: Identify subjects and tissue specimens for biomarker discovery and validation.

- Identify from the existing database at Henry Ford Health System (HFHS) lists of eligible prostatectomy patients as defined in the Research Strategy, confirm availability of banked formalin fixed and paraffin-embedded (FFPE) prostate tissue with biorepositories. Target completion January 31st 2016; Completed January 1st 2016

- Calculate CAPRA-S scores for all eligible subjects. Target completion January 31st 2016; Completed January 15th 2016

- Perform incidence sampling to determine discovery and validation study samples. Target completion September 1st 2016; Discovery sample 100% completed September 1st 2017

- Tumor blocks will be pulled from archive, determination of the optimal block, and sections cut and tumor areas marked by pathologist. Target completion September 1st 2017; Discovery sample pathologic review completed September 1st 2017

- Pathology review of cut cases and slides transferred to UCSF. Target completion January 1st 2018; Discovery sample 100% completed as of September 1st 2018

Major Task #2: Tissue processing and DNA extraction for entire project.

- Manual tumor tissue macrodissection. Target completion January 1st 2018; Discovery sample 90% completed as of September 1st 2018

- DNA extraction and quality assessment. Target completion February 28th 2018; Discovery sample 90% completed as of September 1st 2018

Major Task #3: Perform genomic microarray experiments.

- Carry out array comparative genomic hybridization (aCGH) on Aim 1 DNAs at UCSF. Target completion date September 1st 2017; Agilent reagent quotes obtained. Reagents ordered. 60 samples run and passed QC as of September 1st 2017. As of September 1st 2018, this on hold to see if we can derive both methylation and copy number alterations from the Illumina EPIC arrays.

- Quality control for aCGH and determination of copy number via CBS. Target completion date September 1st 2017; 60 samples run and passed QC as of September 1st 2017.

- Quality control of methylation microarray data and preparation of an analysis dataset. Target completion date September 1st 2017; An initial analysis set of 48 samples has been compiled, QCed and initial analyses have been completed (see next section) as of September 1st 2017. As of September 27th 2018, we have sent our second wave of DNA subjects for methylation arrays, which include 64 specimens. We plan to send our third and final wave of specimens for methylation arrays by January 1st 2019.

- Conduct methylation microarray experiments on Aim 1 DNAs. Target completion date September 1st 2017; Worked out an agreement with Illumina to provide methylation reagents for 1st 48 samples to determine if the Illumina EPIC arrays are going to be useful in also identifying copy number alterations in FFPE preserved prostate tumors from African Americans. The initial results of those analyses did not prove promising, and as part of our second wave of arrays, we including a set of 8 African American prostate normal reference specimens which we believe will improve the quality of the copy number calls from the methylation arrays. Illumina has again provided the additional arrays and reagents for the normal specimens to determine the degree to which these will help facilitate a higher fidelity of copy number calling from methylation arrays. Reagents ordered. Established agreement with a core at USC for array processing. We expect to receive the methylation data from the second wave a array typing in October, and our assessment of agreement should be completed by mid-November 2018.

Major Task #4: Statistical analyses for GEMCaP and published methylation biomarkers. Target completion November 1st 2017; Based on our initial discovery sample set, preliminary analyses for GEMCAP and single CpG sites have been conducted as of September 21st 2017.

Major Task #5: Discovery of African American specific copy number and methylation biomarkers. Target completion Febuary 1st 2018; We have used TCGA data to identify a copy number based biomarker associated with recurrent disease. The manuscript from these analyses is being submitted to Clinical Cancer Research in October 2018.

Major Task #6: Validate integrated biomarker panel in a separate discovery set of African American prostate cancer. Target completion July 1st 2018; not yet started.

Major Task #7: Draft manuscripts for publication.

Manuscript #1: CAPRA-S performance in an African American population. 80% completed as of September 1st 2018.

Manuscript #2: Prostate and breast cancers harbor common somatic copy number alterations that consistently differ by race-ethnicity. Target completion November 2017; 100% completed as of September 28th 2018. This paper will be submitted to Clincal Cancer Research in early October 2018.

What was accomplished under these goals?

In the current reporting period, our major activities continue to be the identification of the study subjects, abstraction of their clinical and pathologic data, acquisition of their FFPE tumor tissue blocks, pathologic review of each case, sectioning of blocks, DNA extraction, and genomic analysis. Additionally, using The Cancer Genome Atlas (TCGA) data, we have made progress on analyses for Aim 2 (the discovery of novel DNA alteration-based markers of biochemical recurrence in African Americans), with the identification of a novel DNA copy number biomarker associated with both prostate cancer recurrence.

Regarding the acquisition of specimens, we have identified all 200 subjects for the discovery cohort, and their tissue blocks have been acquired. Of those, 200 (100%) have undergone pathologic review. However, not all of these subjects achieved our quality control threshold of 60% tumor cellularity. Over this period, we have continued to acquire FFPE tissue samples, and with the review of an additional 80 tumors, we have now acquired the 200 that have the requisite tumor cellularity. Among these subjects, 160 have been sectioned and have undergone DNA extraction. For the 200 validation cohort subjects, we have identified all 200 subjects (100%) of the subjects, and we have currently retrieved FFPE blocks for 130 subjects. To complete the validation cohort, we have determined that we will likely need to utilize the Henry Ford Health System frozen biospecimen repository. To this end, we have identified 40 biochemically recurrent and 40 non-recurrent cases in the repository, which will bring us just over our goal of 200 subjects (100 recurrent and 100 non-recurrent) in the validation sample. Currently, we are continuing with the pathologic review, sectioning, and DNA extraction for the remainder of the FFPE and all of the frozen validation specimens from the study subjects.

In the prior period, we pilot tested the newest Illumina methylation arrays, EPIC, on a subset of 48 subjects (24 with biochemical recurrence and 24 who were biochemical recurrence free at last follow-up). We have recently sent the second wave of specimens for EPIC array analysis. This second wave consists of 56 subjects from our cohort, as well as 8 specimens from normal prostate tissue which will be used to make a final assessment of the degree of fidelity of DNA copy number assessment from the EPIC methylation data. Multiple methods have been developed to call somatic copy number alterations using the Illumina methylation arrays (prior to the Illumina Epic release), with accuracy dependent upon tissue preservation and tumor type. Previously, we reported that using the approach of Feber (Feber et al. 2014) implemented in the ChAMP bioinformatics software and run in case-only mode, the range of the per tumor proportion of aCGH array identified copy number alterations also identified by ChAMP was 0%-86%, with a mean of 29%. There was no obvious trend in these proportions with the number of alterations in each tumor or time since preservation. One clear difference with prior studies is the lack of a normal comparison tissue. In this period, we have obtained a set of appropriate normal, FFPE prostate tissue from our biospecimen repository, and these specimens have been sent for methylation array typing. When we receive this data (expected in mid-October 2018), we will attempt to boost the copy number capture rates utilizing the normal reference specimens as well utilizing additional newer methods for calling copy number alterations from methylation array data.

Finally, as the objective of this proposal is to identify DNA-based alterations that may act as optimal prognostic markers of biochemical recurrence in African American men, we performed a parallel analysis of the copy number alteration data present in TCGA to identify such alterations that differ by race-ethnicity that may help guide our analysis. We reported on this work in our last progress report, and since that time, we have continued to add to that manuscript. Our findings now include a copy number based biomarker based on these race-differentiated copy number alterations that is associated with progression free survival in African American TCGA prostate tumors. In addition to details on these new findings, we provide below a brief overview of our approach and initial findings that led to the discovery of this new copy number biomarker of recurrent prostate cancer (progress on Aim 2), as well as initial validation results in our Henry Ford based cohort.

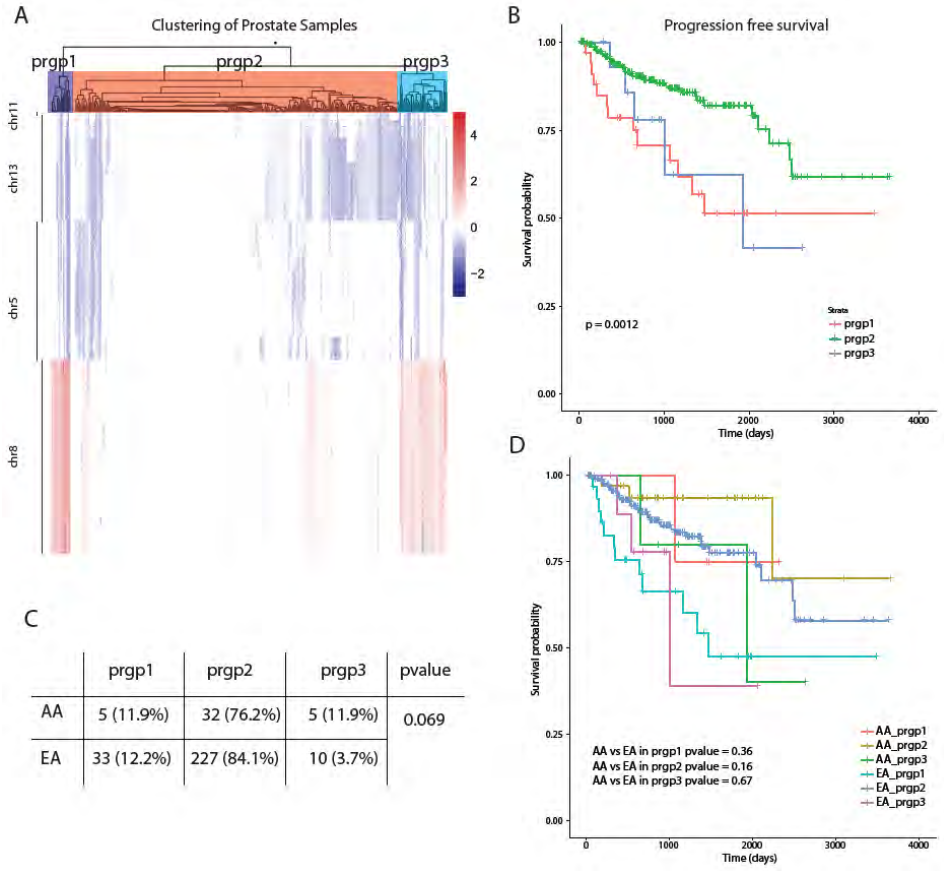
In the 267 European American TCGA prostate tumors, Gistic2 identified 43 copy number alterations. Of these, 17 (39.5%, total 182.8 Mb in length) were amplifications and 26 (60.5%, total 457.7 Mb in length) were deletions. In the 42 African American TCGA prostate tumors, 22 copy number alterations were identified. Of these, 2 (9.1%, spanning 0.11 Mb) were amplifications, and 20 (90.9%, spanning 30.1 Mb) were deletions. These copy number alterations were pooled, resulting in 74 prostate cancer copy number alterations.

Of these 74, 21 (28% of 74; 5 amplifications and 16 deletions) significantly differed by race-ethnicity. In addition, African American prostate tumors contained more extreme copy number alterations at both regions of amplification (80%, 4 of 5) and deletion (81%, 13 of 16). We also used a cross-tumor approach to validate these alterations that differ by race-ethnicity in the TCGA breast tumors. We chose breast cancer because, similar to prostate cancer, it is also a

hormonally driven cancer. A total of nine (42%, 9 of 21) race-differentiated copy number alterations identified in TCGA prostate tumors overlapped with race-differentiated breast cancer copy number alterations. These nine copy number alterations reside on chromosomes 5, 6, 8, 11, 13, and 16. In both tumor types, the chromosome 8q alterations were the sole amplifications and the remaining were deletions. For 6 of the 9 (67%) overlapping copy number alterations, African American prostate and breast tumors both had more extreme alterations. These included two amplification on chromosome 8 and four deletions on chromosome 5, 11, and 13.

To assess the clinical relevance of the identified six race-differentiated SCNAs, we applied unsupervised hierarchical clustering to classify tumors based on the copy number of genes residing in the six race-differentiated SCNAs. Further, we used the Gap statistic (Tibshirani 2001) to identify the number of likely underlying clusters based on the hierarchical clustering result. For the TCGA prostate tumors, three underlying clusters were identified by the Gap statistic, and we refer to these as prgp1, prgp2 and prgp3 (Figure 1A).

Figure 1: Somatic copy number biomarker discovery and association with progression free survival in TCGA prostate tumors.



	prgp1	prgp2	prgp3	pvalue
AA	5 (11.9%)	32 (76.2%)	5 (11.9%)	0.069
EA	33 (12.2%)	227 (84.1%)	10 (3.7%)	

African American (AA) subjects had a higher frequency in prgp3 compared with European Americans (EAs; Figure 1C, 11.9% vs 3.7%, pvalue = 0.069). Clusters prgps 1 and 3 were most

clearly differentiate from prgp2 based on relatively higher levels of 8q gains, which were generally accompanied by higher level losses in the remaining loci in prgp1 relative to prgp3.

Next, we examined whether this underlying heterogeneity in somatic alterations due to differences by race was associated with prostate cancer outcomes. To be most consistent with our study proposal's focus on biochemically recurrent prostate cancer, we evaluated whether 10-year progression free survival (PFS) differed between the identified three copy number defined groups. Clusters prgp1 and prgp3 patients showed worse 10-year PFS compared with prgp2 (Figure 1B, p-value = 0.0012). In a multivariate Cox regression model of PFS including adjustment for race, age-at-diagnosis, Gleason score, and genome-wide copy number load (percentage of the genome with copy number alterations in each tumor), prgp1 and prgp3 subjects had an approximately 2-fold higher risk of recurrent disease in comparison to prgp2 patients (hazard ratio = 2.04, p-value = 0.056). To evaluate whether race specific effects were evident, we also stratified the PFS analyses by race (Figure 1D), and these results demonstrated that there were no significant differences in 10-year PFS by race for each of the underlying copy number defined clusters (Figure 1D).

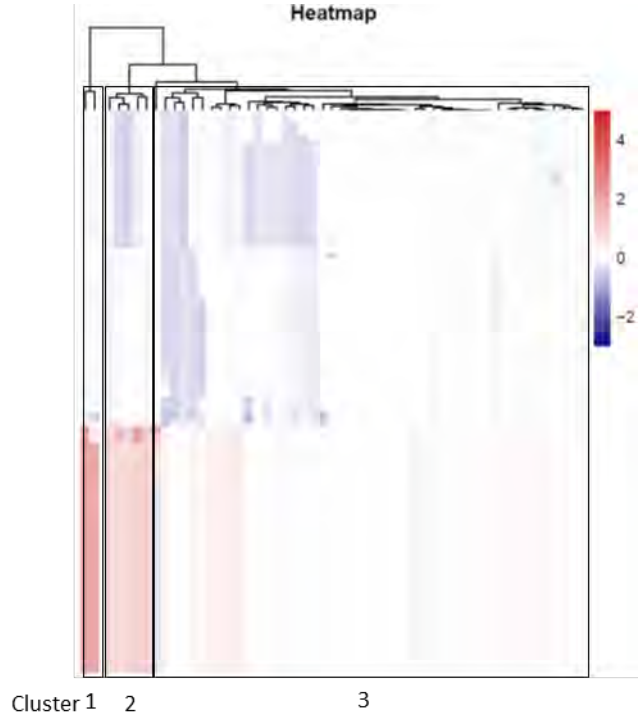
Again, to validate these findings, we used a cross-tumor approach based on breast cancer tumors from TCGA. In comparison to the prostate, two underlying clusters (brgp1 and brgp2) were identified by hierarchical clustering coupled with the Gap statistic, namely brgp1 and brgp2, with brgp2 containing more copy number alterations at the component loci. AAs appeared more frequently in brgp2 compared with EAs (36% vs 25%, p-value = 0.0037). Cluster brgp2 demonstrated worse overall survival (OS; p-value=0.007) and PFS (p-value = 0.049). In a multivariate cox regression model where race, age-at-diagnosis, pathological stage, and genome-wide copy number load were included as covariates, brgp2 patients had an increased risk of death (OS hazard ratio = 1.7, p-value = 0.01) and recurrence (PFS hazard ratio = 1.36, p-value = 0.09) relative to brgp1 subjects. In addition, no significant differences of 10-year OS or PFS were observed between AA and EA breast tumors within either brgp1 or brgp2.

Taken together, these findings demonstrate consistently different tumor biology between AAs and EAs and that these somatic alteration differences have clinical relevance that are independent of both known clinco-pathologic predictors of aggressive disease as well as overall genome-wide copy number alteration burden. We presented our findings at the AACR meeting in Chicago in 2018, and we have recently updated our manuscript, adding the biomarker identification and associations with overall and progression free survival. Given the revised focus on outcomes of prostate and breast cancer, we will be submitting the manuscript to Clinical Cancer Research in October of 2018.

In addition to the discovery based on TCGA, we have also performed a preliminary evaluation of the association between these consistent race-differentiated copy number alterations regions on chromosomes 5, 8, 11, and 13 and prostate biochemical recurrence in our own copy number aCGH data. Using the six regions that define the biomarker, we performed hierarchical clustering coupled with the Gap statistic to determine consistency with the discovery TCGA data, and these findings are presented in Figure 2. Identical to the prostate TCGA data, three underlying clusters were identified in our Henry Ford based data. Clusters 1 and 2 contained two and four subjects respectively. Tumors is these two clusters had the characteristic higher levels

of copy number gain on chromosome 8 observed in prgp1 and prgp3 from the prostate TCGA tumors. Further, in our Henry Ford data, five of the six subjects (83%) in clusters 1 and 2 had recurrent disease. This higher level of recurrence in clusters 1 and 2 relative to cluster 3 is consistent with what we have observed in the discovery TCGA. While this comparison did not reach statistical significance, we are encouraged by the overall consistency of the findings and will attempt to validate this finding in our expanded sample set. Collectively, these findings from both TCGA data and our cohort represent our first discovery (Aim 2) and validation (Aim 3) results for novel DNA based biomarkers of aggressive prostate cancer in African Americans.

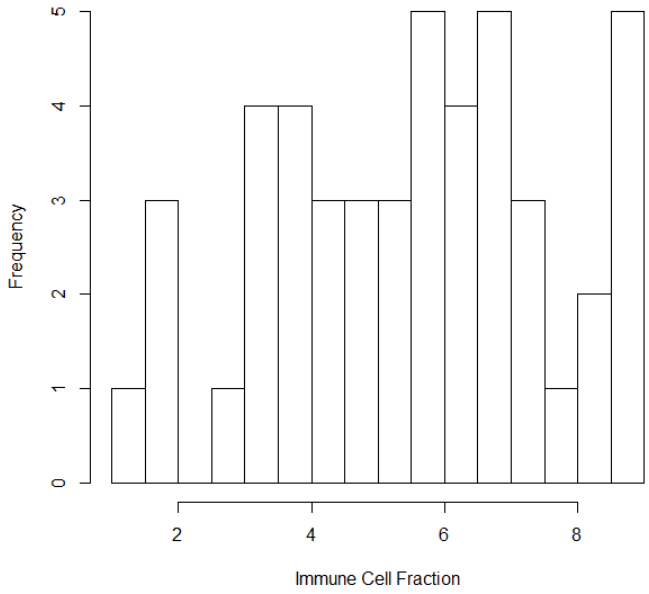
Figure 2: Hierachical clustering of aCGH data in the Henry Ford samples based on the genes in the six race-differentiated regions identified from the discovery TCGA data.



Finally, in preparation for the finalization of our methylation array data and the subsequent analyses, we have continued to explore our first wave methylation array data. Specifically, we have been interested in the estimation of tumor immune cell infiltration from methylation array data. In prostate tumors, immune infiltration has been associated with increased risk of recurrent disease. Most of this work has been done on individuals of principally European ancestry, and there has been little work done to quantify tumor immune infiltration in African Americans via methylation. To estimate the immune cell fraction in each of our tumors, we performed differential analysis to identify differential CpG sites between prostate tissue and blood. From this analysis, we selected the top 1,000 most significant CpGs that are high in tissue and the top 1,000 most significant CpGs that are high in blood. In our data, for each CpGs in each sample, we performed a deconvolution to estimate the immune cells fraction in each tumor. Therefore, for each sample, there were 2,000 estimations of immune fractions, and the mode of the density plot was used to determine the final immune fraction for each sample.

For the Henry Ford sample, the immune cell fractions are presented in Figure 3. These fractions ranged from approximately 1% to 9% in the African American tumors evaluated and were fairly uniformly distributed across the tumors.

Figure 3: Methylation-based immune cell fraction estimates.



Interestingly and consistent with the literature, we found that an increasing immune cell fraction was associated with increased risk of biochemical recurrence in African Americans from our data (hazard rate=1.06, corresponding to each increase of 1% in immune cell fraction, 95%CI 1.00-1.12, p-value=0.051). This effect persisted even after adjustment for the recurrence risk nomogram CAPRA-S (hazard rate=1.07; 95%CI 1.01-1.07; p=0.035), which includes standard clincopathologic predictors of recurrence risk following radical prostatectomy (e.g. diagnostic PSA, Gleason score, margin status, extracapsular extension). These findings are important because they not only give us further insight into the role of immune infiltration in the risk of recurrence in African American men, but they also provide important information for Aim 2, as the optimal construction of a methylation-based classifier of recurrence risk will require the inclusion of an estimate of immune infiltration. Further, these findings suggest an additional area of inquiry. Given that we have the histology slides from our cohort, we can easily go back to have them scored for inflammation by our pathologist based on visual inspection as well as immune cell marker immunohistochemical profiling.

- **What opportunities for training and professional development has the project provided?**

Dr. Paris at UCSF had a summer intern who was part of the UCSF Minority Training Program in Cancer Research. This DoD project allowed the student to gain experience in pathology review, macrodissection and DNA extraction. She also participated in monthly UCSF-Henry Ford team meetings.

- **How were the results disseminated to communities of interest?**

Nothing to report

- **What do you plan to do during the next reporting period to accomplish the goals?**

1. Complete the pathologic review of all 400 tumors; sections for all tumors will be cut and sent to UCSF for macrodissection, DNA extraction, and if needed, copy number array profiling (dependent upon goal #2).
2. Complete a methods manuscript describing the results from a pilot study of 48 tumors (24 with and 24 without biochemical recurrence that are part of the discovery sample) to determine the sensitivity and specificity of the new Illumina EPIC methylation arrays to recover copy number alterations in the tumors, as this has not been reported to date.
3. Conduct all methylation array experiments for the discovery sample.
4. Conduct all analyses for Aim 1 to evaluate how existing DNA-based biomarkers of recurrent prostate cancer reported in the literature apply to African Americans. This includes the completion of a manuscript on the performance of CAPRA-S in African American men and whether its effectiveness differs by genome-wide percent African ancestry.
5. Complete manuscript on the identification of race-differentiated copy number alterations in prostate and breast tumors. This manuscript now includes an evaluation of how these alterations combine into new biomarkers of disease recurrence and overall survival in both prostate and breast cancer. Therefore, this manuscript addresses Aim 2 of our proposal, the discovery of new DNA-based biomarkers of aggressive disease in African Americans.

6. Perform Aim 2 analyses to discovery novel DNA-based biomarkers of recurrent prostate cancer in our cohort of African Americans.
7. Perform Aim 3 analyses to validate the novel biomarkers identified in Aim 2, and complete the corresponding manuscripts describing these results.

4. IMPACT:

a. What was the impact on the development of the principal discipline(s) of the project?

Our initial findings from genome-wide copy number and methylation data suggest that some molecular biomarkers of biochemical recurrence discovered in European American will apply to African American men. However, differences are also apparent and justify discovery of ethnic specific markers African American men.

Our finding of similar effectiveness of CAPRA-S in African American men in comparison to European American men is something that is not established in the literature. These results impact clinical care of African American men with prostate cancer as they establish that CAPRA-S can be used effectively in assessing risk of recurrence in this minority population that suffers disproportionately from prostate cancer.

Our TCGA-based findings have identified race-differentiated copy number alterations in prostate cancer that are consistently race-differentiated in breast cancer, another hormonally driven tumor type. We have further found that these consistently race-differentiated copy number alterations in combination define underlying groups that are associated with both overall and progression free survival in both prostate and breast cancer. These findings demonstrate that there are not only underlying somatic genetic alterations that differ by race-ethnicity and that these alterations are associated with increased risk of aggressive disease and death, even after accounting for overall tumor copy number alteration burden and clinicopathologic predictors of aggressive disease.

b. What was the impact on other disciplines?

Our manuscript using TCGA data that details the race-differentiated copy number alterations that are unique and shared between prostate and breast has a clear impact on the field of breast cancer racial disparities.

In this same manuscript, we developed a new area under the curve method for quantifying copy number alterations and testing with outcomes. This new approach could be used in the analysis of copy number alterations in any tumor type and therefore has impact on cancer research in general.

What was the impact on technology transfer?

Nothing to report

c. **What was the impact on society beyond science and technology?**

Nothing to report

8. CHANGES / PROBLEMS:

a. **Changes in approach and reasons for change**

We have made the decision to not match our biochemical recurrence and non-recurrence subjects on CAPRA-S score as part of the design. Rather, we will adjust for CAPRA-S as part of our analysis to ensure that our biomarker(s) provide added value to CAPRA-S.

To facilitate the completion of our validation sample, we are also including specimens from our frozen tissue repository. As of September 27th 2018, we have identified 80 subjects (40 with biochemical recurrence and 40 without), in our biobank. Our plan is to histologically evaluate a sample pilot (consisting of five specimens) for quality and tumor purity, and utilize this tissue resource to complete our validation sample. Analytically, there will obviously be differences between results generated from FFPE and frozen tumor DNA. To address these differences, we plan to perform separate analyses in samples from the two sources and then combine the results using meta-analysis.

b. **Actual or anticipated problems or delays and actions or plans to resolve them**

The delay for this reporting period is similar to the last. While we have increased our pace, FFPE block retrieval and pathologic review remained a bottleneck. We have worked closely with our colleagues in pathology to solve both issues, this includes our pathologist (Dr. Nilesh Gupta), and we have identified a research pathologist (Dr. Kanika Teneja), who does not have clinical responsibilities. With Dr. Teneja's help, Dr. Gupta has been able to complete the review of the discovery cohort. With this collaborative pathology effort in place (as well as the addition of another pathologist, Dr. Sean Williamson) as well as the additional frozen tissue samples identified above, we are on track to complete the review of all 400 tumors by the April 2018.

c. **Changes that had a significant impact on expenditures**

Nothing to report

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

e. **Significant changes in use or care of human subjects**

Nothing to report

f. **Significant changes in use or care of vertebrate animals.**

Nothing to report

g. **Significant changes in use of biohazards and/or select agents**

Nothing to report

9. PRODUCTS:

a. **Publications, conference papers, and presentations**

Presentation #1 DoD IMPaCT Meeting 2016, Bethesda, MD: The impact of self-identified race-ethnicity and genetic ancestry on a commonly used clinicopathologic predictor of biochemically recurrent prostate cancer.

Presentation #2 AACR Meeting 2018, Chicago, IL: Breast and prostate cancers harbor common somatic copy number alterations that consistently differ by race.

i. **Journal publications.**

Nothing to report

ii. **other non-periodical, one-time publications.**

Nothing to report

iii. **Other publications, conference papers, and presentations.**

Nothing to report

b. **Website(s) or other Internet site(s)**

Nothing to report

c. **Technologies or techniques**

Nothing to report

d. **Inventions, patent applications, and/or licenses**

Nothing to report

e. **Other Products**

Nothing to report

10.PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **What individuals have worked on the project?**

Name:	*Albert M. Levin, PhD*
Project Role:	*co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Dr. Levin is the PI for the Henry Ford site. In addition to the design of the study, he is overseeing the process of tissue acquisition, pathology review, clinical/pathological data abstraction, histological staining and sectioning of the blocks, specimen shipment, data analysis, and manuscript writing.*
Funding Support:	*DoD; The Fund for Henry Ford*

Name:	*Pamela L. Paris, PhD*
Project Role:	*co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Dr. Paris is the PI for the UCSF site, which is doing all of the DNA extractions and copy number array profiling. She is also working closely with Dr. Levin on oversight of pathologic review and tissue preparation, as well as development and writing of manuscripts based on the cohort.*
Funding Support:	*DoD*

Name:	*Benjamin A. Rybicki, PhD*
Project Role:	*co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Rybicki has provided mentorship and guidance for all aspects of the study development for Dr. Levin. He also participates in the development and the writing of manuscripts for the study.*
Funding Support:	*DoD*

Name:	*Nilesh Gupta, MD*
Project Role:	*Pathologist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Gupta is responsible for the pathologic review of all of the tumors from the cohort subjects.*
Funding Support:	*DoD; The Fund for Henry Ford*
Name:	*Sean Williamson, MD*
Project Role:	*Pathologist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Williamson is working closely with Dr. Gupta on the pathologic review of all of the tumors from the cohort subjects.*
Funding Support:	*The Fund for Henry Ford*

Name:	*Kanika Teneja, MD*
Project Role:	*Research Pathologist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Teneja is working with Drs. Gupta and Williamson to increase the pace of review all of the tumors from the cohort subjects.*
Funding Support:	*The Fund for Henry Ford*

Name:	*Yalei Chen, PhD, MS*
Project Role:	*Biostatistican*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Dr. Chen works closely with Drs. Levin and Paris on all analyses of the data generated in this project.*
Funding Support:	*DoD; The Fund for Henry Ford*

Name:	*Sudha Sadasivan, PhD, MPH*
Project Role:	*Study coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Dr. Sadasivan is responsible for the day-to-day management of all aspects of the project.*
Funding Support:	*DoD; The Fund for Henry Ford*

Name:	*Rehnuma Newaz, BA, MPH*
Project Role:	*Laboratory technician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Newaz is responsible for the acquisition of the tumor blocks, abstraction from the original pathologic review to determine within which blocks the index nodule is located, and normal tissue*

	macrodissection, and normal tissue DNA extraction.
Funding Support:	*The Fund for Henry Ford*

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report

c. **What other organizations were involved as partners?**

Nothing to report

11.SPECIAL REPORTING REQUIREMENTS

Not applicable

12. APPENDICES:

Nothing to report