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TITLE: Validation of Metabolomic, Diagnostic, and Prognostic Classifiers of Lung Cancer

PRINCIPAL INVESTIGATOR: Curtis Harris

CONTRACTING ORGANIZATION:
The Geneva Foundation

Tacoma, WA 98402

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14. ABSTRACT

We propose to investigate the performance of previously discovered urinary metabolomic biomarkers among military personnel at high risk for lung cancer, by focusing on early detection, thereby potentially improving its very bleak prognosis. Additionally, global metabolomic profiling will allow us to interrogate whether the military have unique exposures that may be related to lung cancer, which may aid currently existing risk, diagnostic and prognostic lung cancer classifiers in the military populations.

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Urine is a non-invasively collected biospecimen and is abundant, thus allowing for re-sampling, and has proven conducive to biomarker discovery; this biofluid holds a great potential for being clinically useful for diagnosing lung cancer and guiding treatment options. The major goals of this project are to validate previously identified risk, diagnostic and prognostic urinary metabolomic markers of lung cancer in military and veteran populations from the Detection of Early lung Cancer among Military Personnel (DECAMP) consortium and the Walter Reed National Military Medical Center (WRNMMC) Low Dose Computer Tomography Scan Lung Cancer Screening Program. Additionally, the aims are to validate previously established diagnostic classifiers that perform robustly in the African American population: this part of the project will be carried out utilizing urine specimens from the Southern Community Cohort Study, comprising a high number of African Americans. Being that both military populations proposed for evaluation in this study comprise lung cancer patients who had indeterminate lung nodules detected by LDCT, which were subsequently evaluated by other diagnostic methods, we will be able to assess whether metabolomic biomarkers can be utilized to build upon this already existing screening technology to distinguish malignant from benign nodules. The specificity of LDCT is very poor, and our metabolomic classifier may be able to improve this crucial parameter, and also possibly identify those patients who would benefit from chemotherapy, as this is currently controversial for stage IB patients. The third cohort we would utilize in this study is the Southern Community Cohort Study (SCCS), a civilian population with a high prevalence of African American subjects. Considering that the African American population is fast growing in the military ranks, we will be able to assess whether a previously identified 13-metabolite 'group specific' classifier is better at diagnosing lung cancer in African Americans, who have a higher lung cancer prevalence. The result of this part of the study may also illuminate genetic and biological differences that contribute to this health disparity. We consider that the proposed aims in our study would greatly contribute to the mission and specific goals of the LCRP.
Ultimately, the overarching goal is to develop sensitive and specific markers for the early detection of lung cancer, when prognosis is significantly better.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Urine, metabolomics, metabolites, risk, diagnosis, lung cancer, non-small cell lung cancer, serum, plasma, tissue, early detection

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.

- What were the major goals and objectives of the project?

Our study is directly relevant to multiple areas of emphasis put forth by the LCRP, those being: 1) Identification or development of noninvasive or minimally invasive tools to improve detection of the initial stages of lung cancer (urine metabolomic profiling); 2) Identification, development, and/or building upon already existing tools for screening or early detection of lung cancer (LDCT); 3) Identification of innovative strategies for prevention and treatment of early and/or localized lung cancer, and 4) Understanding predictive and prognostic markers to identify responders and non-responders. Our goal is to validate non-invasive metabolomic biomarkers previously shown to be diagnostic and prognostic classifiers in the urine of lung cancer patients when compared to population controls. We are also aiming to build upon those metabolomic classifiers by identifying other risk-associated metabolites, some of which may be unique markers of exposure in the military that may exacerbate smoking-induced lung cancer.

- What was accomplished under these goals?

From September 15 to December 15, we began drafting the MTA agreements with collaborating institutions (Boston University, Walter Reed Medical Center and Vanderbilt University) so that biospecimes can be sent to the Laboratory of Human Carcinogenesis (LHC), NCI, NIH for analysis. Furthermore, we have obtained an exemption from the Office of Human Research Protections (OHRP) at the NIH, allowing us to conduct the projects described in this award using the biospecimens from the collaborating institutions without a prior IRB approval. Additionally, we also received an approval from the US Army Medical Research and Material Command Office of Research Protections to conduct the described experiments.
From December 15 to March 15, we were able to execute Material Transfer Agreements (MTAs) with collaborating institutions (Boston University, Walter Reed Medical Center and Vanderbilt University) in order for the biospecimens to be sent to the Laboratory of Human Carcinogenesis (LHC), NCI, NIH for analysis.
A post-baccalaureate student was mentored and additionally trained to conduct the proposed research, under the supervision of the key investigators.
Methods were developed for the designated instrument (Waters TQ-S micro), and methods were optimized in order for the instrument to be fully operational upon the receipt of the biospecimens described in this project.

From March 15 to June 15, we were able to receive DECAMP-1 urinary specimens (blinded and de-identified) from our collaborators at Boston University. Furthermore, we were able to communicate and agree on the details of specimen aliquoting from Walter Reed, that are in the process of being prepared to be sent to us, Laboratory of Human Carcinogenesis, NCI, NIH. Additionally, we were able to optimize the mass spectrometry methods and to test the instrument sensitivity that will be used for the quantitation of metabolites of interest as described under this award.
From June 15 to present, we have been able to establish contact with Dr. Justin M. Wells, Biobank Director of the Military Clinical Trials Network Biobank at the John P. Murtha Cancer, who is working with his time to send us stage I adenocarcinoma tissues and corresponding urine, serum and plasma samples. Once this samples are received, we will commence mass-spec based measuring of metabolites in all samples comprising this project, and the data will then be analyzed.

- What opportunities for training and professional development did the project provide?

Dr. Majda Haznadar, staff scientist in the LHC who spearheads metabolomics studies, has become proficient in using a Waters triple quadrupole mass spectrometry instrument that is crucial for completion of this project. The funds from this project enabled her to further her professional development in this manner. Furthermore, she has mentored a stellar post-bac student, Christopher M. Diehl, who was hired under this project, and whose salary was covered by the funds of this grant, to help with organization, sample logging, sample processing, etc. Mr. Diehl's experience in LHC and specifically on this project have provided him with exceptional professional development, which helped with his admittance to medical school that he is currently attending.

- How were the results disseminated to communities of interest?

Results will be disseminated in a form of presentations at national and international meetings, as well as by publishing manuscripts comprising the data generated from this project.

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

In the near future when the WRNMMC samples are received by the LHC, we will commence the last portion of this project, which is acquisition and analysis of the data. Dr. Qiyin Cai from Vanderbilt University was sub-contracted as a biostatistician to aid in data analysis and interpretation, and his extensive expertise will be utilized and will be crucial for the correct analysis and interpretation.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Goal 1: IRB approvals—100% completion

Goal 2: Staff hiring—100% completion

Goal 3: Global metabolomics profiling—60% completed, as DECAMP-1 and SCCS samples have been sent to LHC. We are awaiting receipt of WRNMMC samples, and expect to receive them by mid-November 2016. Sample profiling will commence as soon as WRNMMC are received by LHC.

Goal 4: Data processing and analysis of global metabolomics data—0% completion

Goal 5: Targeted metabolomics profiling—0% completion

Goal 6: Data processing and analysis of targeted metabolomics data—0% completion

Generally, the goals will not change from one reporting period to the next and are unlikely to change during the final reporting period. However, if the awarding agency approved changes to the goals during the reporting period, list the revised goals and objectives. Also explain any significant changes in approach or methods from the agency approved application or plan.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the

project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

The following subtask were accomplished under the above-described goals:

- IRB exemption was prepared, submitted and granted for the exemption for DECAMP, Murtha Cancer Center (WRNMMC) samples so that LHC may commence and complete the proposed studies HRPO approval was received from the US Army Medical Research and Material Command Office of Research Protections so that LHC may commence and complete the proposed studies
- A post-bac student was hired and trained to handle, log and process the samples for the metabolomic profiling; he was crucial for developing an automated method using a liquid-handling robot for the samples to be processed
- Samples were received and processed from Boston U (DECAMP-1) and Vanderbilt U (SCCS)

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Dr. Majda Haznadar, staff scientist in the LHC who spearheads metabolomics studies, has become proficient in using a Waters triple quadrupole mass spectrometry instrument that is crucial for completion of this project. The funds from this project enabled her to further her professional development in this manner, by mastering a technology that will be applicable in our future studies as well. Furthermore, she has mentored a stellar post-bac student, Christopher M. Diehl, who was hired under this project to help with organization, sample logging, sample processing, etc. Mr. Diehl's experience in LHC and specifically on this project have provided him with exceptional professional development, which helped with his admittance to medical school that he is currently attending.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

NOTHING TO REPORT.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

For the next reporting period, we are planning on receiving WRNMMC samples from Dr. Justin Wells, Walter Reed National Military Medical Center Biobank Director, and his team who are in the process of preparing them, along with accompanying demographic and clinical information. We are then planning on completing the following major goal as described in the SOW:

Major Goal 3 (currently 60% completed): global metabolomic profiling of all three cohorts comprising the study: DECAMP-1, SCCS and WRNMMC

4. IMPACT: This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period. Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

- the development of the principal discipline(s) of the project;
- other disciplines;
- technology transfer; or
- society beyond science and technology.

As we have not acquired the data yet, we cannot discuss impact in the context of our findings. However, we can discuss the impact we foresee stemming from the projects comprising this award. No biomarkers have been developed to date that can successfully complement currently available screening modalities for detecting early stage lung cancer. Low dose CT (LDCT) has been proven to be more successful at reducing lung cancer mortality, by 20%, than chest X-ray. While no lesion goes undetected by LDCT, most of them are non-malignant. In fact, the false discovery rate of LDCT is astonishingly high at 96.4%. We have previously described four metabolomic markers detected in the urine of lung cancer patients compared to non-diseased population controls. These markers have shown to be robust at both detecting lung cancer, and predicting survival. While we have carried out a series of validation steps to show that these markers may have strong clinical utility, i.e. by quantitating their measurements at two time points over two years apart and showing high intraclass coefficients >0.85 that indicates their possible clinical utility, external validations are required. Furthermore, by assessing established military trials, we may be able to show clinical utility of previously described metabolomic biomarkers in the military personnel, veterans, and their families. In the studies proposed herein, we would assess metabolomic biomarkers in the following military cohorts: Detection of Early lung Cancer among Military Personnel (DECAMP) consortium, and Walter Reed National Military Medical Center (WRNMMC) Low Dose Computer Tomography Scan Lung Cancer Screening Program. Both cohorts consist of patients who had indeterminate pulmonary nodules detected by LDCT, some of which were confirmed to be cancer. However, we may be able to avoid downstream diagnostic testing in some patients by utilizing urinary metabolites that may be able to distinguish malignant from non-malignant nodules, thereby complementing LDCT screening modality. Two of four metabolites are expressed at a higher level in tumor compared to non-tumor lung tissue, and may indeed be able to identify malignant nodules. Positive results of the research outlined here would have immediate impact on the military populations at high risk for developing lung cancer, but also on the general population, being that we are utilizing well established clinical trials with established protocols and available biospecimens. The results of this research may indicate that metabolomic biomarkers investigated herein may be a robust complement to LDCT in detecting lung cancer early with a higher specificity than LDCT alone, thereby avoiding over-diagnosis and potential complications from downstream diagnostic tests, and high costs associated with such methods. Long term, we would investigate whether these biomarkers can be used to predict which patients would benefit from chemotherapy, as this is currently controversial in stage IB patients. For this, we will be able to utilize samples currently being accrued by protocol 2 of DECAMP. Furthermore, a ‘group specific’ metabolite profile will be assessed in a civilian Southern Community Cohort Study (SCCS) comprising a high number of African American subjects, population with a higher incidence of lung cancer. This ‘group specific’ classifier may be more robust at diagnosing lung cancer in this population, but may also unravel biology that may explain such health disparity. We consider that the results from the study proposed here may lead to a development of a test complementary to LDCT that may increase its specificity and ultimately improve lung cancer prognosis, decrease over-diagnosis and costs associated with expensive and potentially unnecessary diagnostic tests.

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal isciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

How the field or discipline is defined is not as important as covering the impact the work has had on knowledge and technique. Make the best distinction possible, for example, by using a “field” or “discipline,” if appropriate, that corresponds with a single academic department (i.e., physics rather than nuclear physics).

NOTHING TO REPORT.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

NOTHING TO REPORT.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

NOTHING TO REPORT.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- improving social, economic, civic, or environmental conditions.

NOTHING TO REPORT.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

- Changes in approach and reasons for change.
- Actual or anticipated problems or delays and actions or plans to resolve them.
- Changes that have a significant impact on expenditures.
- Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

The only change that took place since the last reporting period is that the leading PI on the collaboration with Walter Reed is now Dr. Christina Brzezniak. These changes were reported to Mrs. Amanda C. Carrera, the Grants Management Specialist appropriately and all documents were updated. The reason for change is the unexpected retirement of Dr. Corey Carter from Walter Reed.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes.
Remember that significant changes in objectives and scope require prior approval of the agency.

Unexpected retirement of Dr. Corey Carter from the military.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

NOTHING TO REPORT.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

NOTHING TO REPORT.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

NOTHING TO REPORT.

6. PRODUCTS: List any products resulting from the project during the reporting period. Examples of products include:

- publications, conference papers, and presentations;
- website(s) or other Internet site(s);
- technologies or techniques;
- inventions, patent applications, and/or licenses; and
- other products.

If there is nothing to report under a particular item, state "Nothing to Report."

NOTHING TO REPORT.

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award. There is no restriction on the number. However, agencies are interested in only those publications that most reflect the work under this award in the following categories:

Journal publications. List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Include any peer-reviewed publication in the periodically published proceedings of a scientific society, a conference, or the like. A publication in the proceedings of a one-time conference, not part of a series, should be reported under "Books or other non-periodical, one-time publications."

Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Books or other non-periodical, one-time publications. Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like.

Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Other publications, conference papers, and presentations. Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;
- biospecimen collections;
- audio or video products;
- software;
- models;
- educational aids or curricula;
- instruments or equipment;
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- clinical interventions;
- new business creation; and
- other.

NOTHING TO REPORT.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Provide the following information on participants:

- what individuals have worked on the project?
- has there been a change in the other active support of the PD/PI(s) or senior/key personnel since the last reporting period?
- what other organizations have been involved as partners?

1. Name: Majda Haznadar, PhD
Project Role: Staff Scientist, Co-Principal Investigator
Nearest person month worked: 5
Contribution to Project: Dr. Haznadar worked on receiving NIH and US Army HRPO approvals, aided in MTA agreements placed with collaborating institutions, conducted interviews and was involved in the hire of a new fellow (post-bac) and trained the fellow, was trained on handling the liquid handling robot and the LC-MS instruments, and is involved with all the aspects of the project, as well as guiding and reporting on the project progress. o salary was covered by the funds of this grant.

2. Name: Curtis C. Harris, MD
Project Role: Lab Chief, Principal Investigator
Nearest person month worked: 5
Contribution to the Project: Dr. Harris hired a new post-bac fellow, has guided all the progress of the described aims of the project, and has maintained constant contact with collaborating institutions, ensuring project progress. No salary was covered by the funds of this grant.

3. Name: Christopher Diehl
Project Role: Post-bac fellow
Nearest person month worked: 5
Contribution to the Project: Mr. Diehl was hired and trained to operate the liquid handling robot, and to handle all the specimens described in the project. Mr. Diehl's salary was covered by the funds of this project, as described in the budget.

4. Name: Avrum Spira, MD
Project Role: Co-Investigator from Boston University
Nearest person month worked: 3
Contribution to the Project: Dr. Spira has worked on establishing MTA agreements and IRB protocols for the metabolomic analysis of specimens from the DECAMP-1 DoD funded consortium and will be providing the samples for the analysis. No salary was covered by the funds of this grant.

5. Name: Previously Corey Carter, MD; Now Christina Brzezniak, MD
Project Role: Co-Investigator from WRNMMC
Nearest person month worked: 3
Contribution to the Project: Dr. Carter has worked on establishing MTA agreements and IRB protocols for the metabolomic analysis of specimens from the WRNMMC cohort. As Dr. Carter had retired, Dr. Christina Brzezniak

has taken over the leading role in coordinating our collaboration with Walter Reed. No changes to the actual funding were made or will be necessary, as Dr. Brzezniak's salary will not be covered by the funds of this grant. The level of effort and specific aims remain the same as they were for Dr. Corey Carter.

6. Name: David Schrump, MD
Project Role: Co-Investigator from the NIH Clinical Center (NCI)
Nearest person month worked: 1
Contribution to the Project: Dr. Schrump has been guiding the progress of the project, due to his extensive clinical experience, and has been the key advisor on the awarded projects. No salary was covered by the funds of this grant.

7. Name: Frank Gonzalez, PhD
Project Role: Co-Investigator from the NCI, NIH
Nearest person month worked: 3
Contribution to the Project: Dr. Gonzalez is providing one of the mass spec instruments for future analysis of the samples approved under the current award (Waters qTOF LC-MS instrument for global metabolomics profiling), and has provided personnel time of his mass spectrometrist, Mr. Kristopher Krausz, who trained Dr. Haznadar to operate the mass spectrometry instrument that was purchased and designated specifically for this project—Mr. Krausz will continue to supervise mass spec analyses of the samples. Dr. Gonzalez has provided extensive metabolomics experience in guiding the ongoing projects described in this award. No salary was covered by the funds of this grant.

8. Name: Qiuyin Cai, PhD
Project Role: Sub-contracted from Vanderbilt University
Nearest person month worked: 3
Contribution to the Project: Dr. Cai will provide extensive biostatistics experience to guide the analysis of the results stemming from the planned metabolomics analyses; sub-contract was put in place with Vanderbilt to carry out this work, as described in the budget.

9. Name: William Blot, PhD
Project Role: Co-Investigator
Nearest person month worked: 3
Contribution to the Project: Dr. Blot is a head investigator of the SCCS study, and is providing Southern Community Cohort Study (SCCS) urine samples and will be instrumental in guiding the epidemiological conduct of the studies proposed herein. No salary was covered by the funds of this grant.

10. Name: Neil Caporaso, MD
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to the Project: Dr. Caporaso has provided and will continue to provide key feedback to the epidemiological, statistical and overall scientific progress of this awarded proposal. No salary was covered by the funds of this grant.

What individuals have worked on the project? Please see above.

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

• Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project and with what funding support. If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g., ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-control and constrained coding

Funding Support: The XYZ Foundation (Complete only if the funding support is provided from other than this award.)

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission.

Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

The only change that took place since the last reporting period is that the leading PI on the collaboration with Walter Reed is now Dr. Christina Brzezniak. These changes were reported to Mrs. Amanda C. Carrera, the Grants Management Specialist appropriately and all documents were updated. The reason for change is the unexpected retirement of Dr. Corey Carter from Walter Reed.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed. Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

8. SPECIAL REPORTING REQUIREMENTS: None

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent study questionnaires, and surveys, etc. Study questionnaires, and surveys, etc.