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TITLE: Genomics of Early Lung Cancer Among Military Personnel (GELCAMP)

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14. ABSTRACT
Lung cancer is a leading cause of death worldwide, and improvements in morbidity and mortality hinge on continued investigation into the biology of cancer. Whole genome sequencing can uncover cancer-associated mutations that can meaningfully impact clinical care and decision-making. In this study, blood, bronchial epithelial cells and tumor tissue (as applicable) will be sequenced from 50 cases with confirmed cancer and 50 non-cancer controls. The resulting profiles will be analyzed for genetic markers that that may enable earlier diagnosis, guide therapy decisions and improve patient outcomes.

15. SUBJECT TERMS
Lung cancer, whole genome

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- **INTRODUCTION:**

  Currently several biomarkers are being validated on the DECAMP specimen, but none of these use the whole genome sequencing (WGS) technology. WGS offers a novel view of mutational changes in early lung cancer. We are testing for genomic biomarkers for the detection of early lung cancer using whole genome sequencing of DNA specimens from blood, endobronchial brushings and lung tumor specimens (for those with lung cancer). While genomic testing of lung cancer has been performed in other studies, testing other sites within the lung as well as peripheral blood for these biomarkers has not been attempted. The DEAMP cohort is unique for several reasons. The DECAMP cohort is the only cohort that specifically enrolls military personnel and offers the potential to identify mutations that might be linked to military specific exposures. It is also one of the most comprehensive and detailed cohorts associated with bronchoscopic brushings and tissue matched with CT imaging, clinical history in a longitudinal cohort.

- **KEYWORDS:**
  Cancer
  Lung
  Biomarkers
  Genomic
  Genome
  Tumor
  DNA
  Whole Genome Sequencing
  WGS

- **ACCOMPLISHMENTS:**
  - **What were the major goals of the project?**
    - Aim 1: Evaluate DNA copy number alterations and somatic mutations in the airway and tumor as well as germline polymorphisms that can distinguish benign vs. malignant nodules**.**
    - Aim 2: Characterize DNA copy number alterations and somatic mutations in the airway and tumor that associate with prognosis among those with lung cancer.

  - **What was accomplished under these goals?**
    - Acquired WRNMMC and USU IRB approval for amended protocol
    - Addressed HPRO's questions and request for additional information
    - Completed and executed WRNMMC DRP Data Sharing Agreement and Site System Verification
    - Received WRNMMC DRP start letter
    - Successfully transitioned and onboarded Clinical Trial Coordinator and Clinical Research Assistant (Data Analyst) as HJF employees as American College of Radiology was unable to fulfill onboarding requirements

- **What opportunities for training and professional development has the project provided?**
  - Nothing to Report.

- **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?**
  - Obtain HPRO final approval and begin research activities
  - Obtain USU approval for budget allocation from ODC (Vendor contract with American College of Radiology) to Personnel
  - Finalize iMedidata Rave access
  - Modify existing USUHS array processing SOP for GELCAMP protocol
  - Finalize existing DECAMP shipping SOP for GELCAMP requirements
  - Modify and finalize data tracking / sharing mechanism between WRNMMC and USUHS
  - Modify and maintain electronic mail distribution lists and postal directories for correspondence and communication between the coordinating center and subcontractors and service providers
  - Continue operational teams and routine teleconferences to discuss study progress and timelines

- **IMPACT:**
  - **What was the impact on the development of the principal discipline(s) of the project?**
    - Nothing to Report.

  - **What was the impact on other disciplines?**
    - Nothing to Report.

  - **What was the impact on technology transfer?**
    - Nothing to Report.

  - **What was the impact on society beyond science and technology?**
    - Nothing to Report.

This project will leverage biospecimens and patient outcomes from the DECAMP trial which specifically enrolled military beneficiaries and then perform WGS at the DOD's USUHS Genomics center to find DNA biomarkers which can identify patients who have or will develop lung cancer prior to presentation with concerning clinical or radiographic findings. Biomarkers that can identify individuals with preclinical lung cancer or those at highest risk for developing lung cancer with sufficient sensitivity and specificity could be used to identify individuals who might benefit from increased lung cancer surveillance ultimately leading to earlier lung cancer diagnosis and improved lung cancer outcomes. Additionally, these biomarkers could also be used to identify the subset of individuals most likely to benefit from lung cancer chemoprophylaxis and thereby increase the efficiency of clinical trials seeking to

evaluate novel agents for lung cancer chemoprevention as well as potentially *serve* as intermediate endpoints of therapeutic efficacy in those trials.

In addition, the GELCAMP WGS dataset will serve as a valuable resource for future lung cancer research in several major respects. The GELCAMP benign nodule cohort will provide the first observation of naturally occurring somatic mutation in the lung that does not progress to malignancy. Lung tumor genome analysis is complicated by the high environmentally-caused DNA damage (e.g. smoking) in which it is difficult to separate causative DNA alterations from incidental alterations. In particular, this challenge is the greatest in noncoding genomic regions, which have not yet been studied in detail due to a lack of WGS lung cancer cohorts. The GELCAMP benign nodule cohort will provide this mutational background source that can serve as a powerful control for this separation of causative versus incidental DNA alterations in future studies. Second, the combination of the GELCAMP benign and malignant cohorts will enable new genomic predictors to be constructed that will assign malignancy risk scores to future patient's nodule specimens, based on their genomic alteration profile**.**

- **CHANGES/PROBLEMS:**
  - **Changes in approach and reasons for change**
    - Nothing to Report.
  - **Actual or anticipated problems or delays and actions or plans to resolve them**
    - Following HPRO's determination of non-exempt status, the amended protocol was submitted to WRNMMC for re-review. Despite the study team's efforts to address stipulations quickly and continuously follow-up, we experienced further protocol approval delays in the past year. The amended protocol was resubmitted to WRNMMC DRP at the end of Year 1 (April 2018) but approval was not received until Quarter 2 of this year (October 2018). Additional delays were experienced with USU secondary approval. The protocol was forwarded to USU in October 2018 with request for deferral to HPRO. However, it was decided that the protocol must undergo full IRB approval and USU approval was not received until Quarter 4. The protocol is currently with HPRO for final approval.
  - **Changes that had a significant impact on expenditures**
    - Delays in protocol approval have delayed collaborators contributions**.**
  - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
    - Nothing to Report.

- **PRODUCTS:** Nothing to Report.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
  - **What individuals have worked on the project?** Individuals supporting the project for the past year in excess of 160 hours are:
    - Dr. Robert Browning, PI
    - Maggie Nellissery, Coordinator

- **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.

- **What other organizations were involved as partners?**
    - Uniform Services University, Bethesda MD
        - Bethesda MD
            - Facilities: The American Genome Center
            - Collaboration: Dr. Clifton Dalgard
    - Brown University, Providence, RI
            - Collaboration: Dr. Fenghai Duan (no contributions thus far due to protocol delay)
    - American College of Radiology, Philadelphia, PA
            - Provide analyst and coordinator at WRNMMC via a vendor contract
            - This vendor contract was ended effective March 14, 2019. The coordinator and analyst previously with ACR have been transitioned to HJF.

- **SPECIAL REPORTING REQUIREMENTS**
    - COLLABORATIVE AWARDS: Nothing to Report

- **APPENDICES:**
    - Quad Chart

Genomics of Early Lung Cancer Among Military Personnel (GELCAMP)

Funding Opportunity: DHA-16-CRII-PMRA

PI: Robert F. Browning Jr., M.D., FCCP **Org:** Walter Reed National Military Medical Center **Award Amount:** $954,144

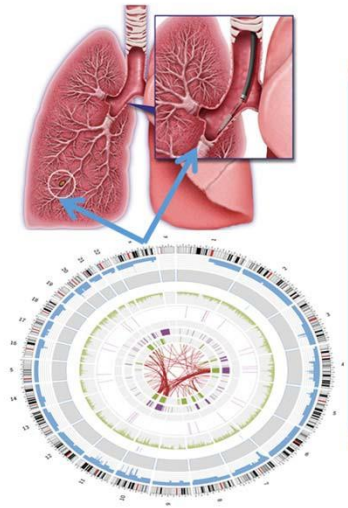
Study/Product Aim(s)

- Primary aim: identify airway genomic alterations in military personnel with early lung cancer that may be used as a biomarker for early diagnosis or screening.
- Secondary aim: identify genomic alterations in the airway or tumor that are prognostic in terms of predicting tumor aggressiveness among those with early stage lung cancer.

Approach

Lung cancer is a leading cause of death worldwide, and improvements in morbidity and mortality hinge on continued investigation into the biology of cancer. Whole genome sequencing can uncover cancer-associated mutations that can meaningfully impact clinical care and decision-making. In this study, blood, bronchial epithelial cells and tumor tissue (as applicable) will be sequenced from 50 cases with confirmed cancer and 50 non-cancer controls. The resulting profiles will be analyzed for genetic markers that that may enable earlier diagnosis, guide therapy decisions and improve patient outcomes.

GELCAMP Whole Genome Study



This study will utilize whole-genome sequencing of blood, bronchial epithelial cells and tumor tissue to identify biomarkers that may lead to earlier diagnosis and improved clinical outcomes in lung cancer.

This project leverages the biorepository created by DECAMP-1 to further investigate gene signatures associated with early lung cancer.

Samples from ~100 participants will be coordinated with up to two years of clinical follow-up data to correlate genetic mutations with outcomes.

Timeline and Cost

	CY17	CY18	CY19
Develop protocol and obtain HRPO, IRB approval			
Identify participants			
Data collection - Clinical			
Data collection - Biospecimens			
Data Processing – Biospecimen Arrays			
Data Analysis – Clinical & Arrays			
Report Results / Publication			

Estimated Budget: $954,144

Updated: 15 APR 2019

Goals/Milestones

CY17 Goals

- Develop protocol and obtain approval from HRPO, IRB
- Set up data management infrastructure to collect clinical data

CY18 Goals

- Obtain approval from HRPO, IRB
- Initiate clinical data collection
- Initiate selection of biospecimens

CY19 Goals

- Complete biospecimen selection and transfer to USU for WGS sequencing
- Complete assay analysis
- Perform statistical analysis
- Prepare manuscript(s) for publication
- Publish study results

Budget Expenditure to date: $13,604.14
Remaining Balance: $940,539.86