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TITLE: Noninvasive Characterization of Indeterminate Pulmonary Nodules Detected on Chest High-Resolution Computed Tomography

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14. ABSTRACT

Lung cancer accounts for more cancer-related mortality than breast, prostate and colon cancer combined, and greater than half of lung cancer cases are diagnosed at advanced stages. Both the National Lung Screening Trial (NLST) and Nederlands-Leuvens Longkanker Screenings ONderzoek (NELSON) trial have demonstrated that low dose CT screening (LDCT) reduces mortality in high-risk patients. Implementation of LDCT screening has however been challenging.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Over 1.5 million incidentally and screening-identified indeterminate lung nodules are identified each year in the US, over 96% of which are benign. A small fraction, however, are malignant and early and accurate characterization of these malignant nodules offers an opportunity for early and potential curative treatment. Current predictive models to discriminate benign from malignant nodules are suboptimal, leading to unnecessary invasive procedures, delayed diagnosis, and thus increased morbidity, mortality and healthcare costs. In this project, we aimed to leverage our experience developing radiomic models to characterize lung nodules using the largest lung cancer screening trial, the National Lung Screening Trial, as training set using a machine learning algorithm. This model, based on quantitative imaging signatures associated with malignancy, was then validated on three external validation cohorts: the DECAMP1 dataset, the Lung Tissue Research Consortium dataset and the Vanderbilt Lung Nodule dataset. As lung cancer affects veterans and military personnel disproportionately, this project is particularly relevant to that patient population.

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

Lung cancer, Radiomics, Lung cancer screening, Chest computed tomography, Biomarker, Lung nodules.

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

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.

Aim 1 (first year of the grant): The first aim of this grant was to develop a CT-based radiomic model using quantitative volumetric analysis of screen-identified lung nodules (model 1), and a combined clinical-radiologic model (model 2) to differentiate benign from malignant nodules.

a. Milestone: development of optimized quantitative radiological variables predictive of the benign or malignant character of lung nodules from a cohort isolated from the NLST (12 months – October 2016). Due to delayed subcontract between Mayo Clinic and Vanderbilt University, the identification of optimization of quantitative radiological variables was completed by October 2017.
b. Milestone: development of a radiologic prediction model (12 months). The radiologic model was completed by October 2017.
c. Milestone: development of a combined clinical/radiologic prediction model (12 months). The clinical/radiologic model was completed by October 2017, but addition of clinical variables did not contribute significantly to the diagnostic test performance of the model and therefore was not selected as the final predictive model in subsequent validations.

Aim 2 (second year of the grant): the second aim of this grant was to prospectively validate the models developed in Aim 1 in the DECAMP-1 dataset (500 patients with indeterminate pulmonary nodules**,** DECAMP PROTOCOL ACRIN 4703).

Milestone: Validation of a radiologic and combined clinical/radiologic prediction models (**Year 2 of the grant**). Enrollment into the DECAMP-1 study was considerably delayed and eventually halted before the expected enrollment of 500 patients at the end of February 2020. This completion of enrollment was anticipated by December 2015 at the time of our application (August 2014), as 125 of the planned 500 patients had already been enrolled. As of October 2021: 489 patients had been recruited to DECAMP-1 (enrollment completed) and nodules have been adjudicated. Due to delayed contracting with DECAMP, the COVID-19 pandemic, and the unexpected death of a colleague running the laboratory in which DECAMP images were to be processed, curated and analyzed (Massion Lab), only 274 nodules (183 malignant and 91 benign, confirmed) could be used for validation of our radiomic model. and using our radiologic model yielded an AUC of 0.66 (strict validation) and 0.74 (loose validation).

We did secure two alternative validation sets, including (1) a validation cohort from the lung nodule registry at Vanderbilt University Medical Center/Nashville Veterans Administration Tennessee Valley Healthcare system (primary investigator: Dr. Pierre Massion, see below) comprised of 91 malignant lung nodules and 79 benign lung nodules (total n=170), as well as (2) the lung nodule cohort from the Lung Tissue Research Consortium (LTRC), comprised of 88 benign and 89 malignant nodules (total n=177). Similar to the early DECAMP-1 cohort, the LTRC cohort was considered "high-risk" as all nodules were evaluated by expert radiologists and felt to be suspicious enough for malignancy to require surgical resection (see below). The validation from the LTRC dataset was reported in a previous report and is summarized below. Funds from this award were not used for these external validation sets. The no-cost extension was solely requested to complete the proposed project to validate our mode on the DECAMP-1 dataset.

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.

Year 1 (for additional details see prior annual report): Nodule selection

As previously reported, participants for our project were selected from the pool of eligible participants in the NLST, who did not withdraw from follow-up, in the CT arm of the study (N=26,262) and included all screen-detected lung cancer cases. Non-lung cancer controls were selected as a stratified random sample from all participants in the pool defined above who were not found to have lung cancer during the screen or follow-up periods of the NLST in a 1:1 fashion. We restricted our analysis to nodules with a size defined by a largest diameter comprised between 7 and 30 mm as reported in the NLST database, as these represent the size criteria used as eligibility criteria in the DECAMP-1 study. CT dataset image transfer, segmentation and analysis have been previously reported.

Nodule segmentation and analysis

The lung nodules were segmented manually using the ANALYZE software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), as previously reported. A comprehensive set of automatically computable, quantitative radiomic metrics was included for the development of a multivariable predictive model to discriminate benign from malignant lung nodules. Based on previous data and preliminary analysis, we considered metrics within the following categories: general characteristics of the nodule (volume and location), nodule characteristics (texture and surface characteristics) and nodule-free surrounding lung characteristics.

Year 2 (for additional details see prior annual report):

Multivariate analysis was performed using least absolute shrinkage and selection operator (LASSO) method. To increase the stability of the modeling, LASSO was run 1,000 times and the variables that were selected by at least 50% of the runs were included into the final multivariate model. The bootstrapping method was then applied for the internal validation, and the optimism-corrected AUC was reported for the final model.

Results:

After exclusion of cases lacking HRCT data, cases with no apparent lesion on last HRCT prior to the cancer diagnosis, cases with nodules invading the mediastinum, cases with missing outcome data, and lesion with size < 7mm or >30 mm, 408 LDCT scans with malignant nodules were selected and analyzed. A stratified random sample of non-lung cancer controls (nodules with size comprised between 7 and 30 mm) was selected on a 1:1 basis, and after exclusion of HRCT containing more than one nodule, 318 nodules were selected and included in the analysis.

The demographic and clinical characteristics of individuals included in the study are summarized in table 1.

Multivariate analysis

In order to select the optimal variables across a set of pre-selected 57 variables previously shown to be predictive of malignancy, adjust the regression coefficients to optimize the transportability (external validity) of the model and determine the degree of optimism of the model and perform optimism-corrected analysis of the performance of the model by ROC analysis, all 57 variables were included in the LASSO regression model. Multivariate analysis using LASSO on all features yielded a multivariate model with 8 selected features (selected with frequency > 50% after introducing bootstrap to reduce variability after 1000 runs) with an AUC estimate of 0.941. These 8 features include: 1. centroid_Z, 2. Min Enclosing Brick, 3. flatness, 4. SILA_Tex, 5. Max_SI, 6. Avg_SI, 7. Avg_PosMeanCurv and 8. Min_MeanCurv, all with $P<0.01$. To correct overfitting (internal validation) we used the bootstrapping technique to estimate the optimism of the AUC. **The optimism-corrected AUC is 0.939**.

Centroid_z captures the location of the nodule in the lung (vertical axis), the **minimal enclosing brick** and **flatness** capture volume and shape, respectively, **Sila_Tex** is a summary variable capturing the degree of abnormality based on texture density within the nodule, **maximum** and **average shape index (Max_SI and Avg_SI)** capture the complexity of the nodule surface and **Average positive mean curvature and (Avg_PosMeanCurv)** and **Minimum mean curvature (Min_MeanCurv)** represents the degree of curvature of the outer surface of the nodule.

We then added variables independently associated with an increased risk of lung cancer in our cohort (age and pack-years). The optimism-corrected AUC for model 2 is 0.941, not significantly different that model 1 (radiomic model).

Table 1. Demographics and Clinical Characteristics of Cancer and Control (n = 726)

	Lung Cancer Cases (n=408)	Nodule-Positive Controls (n=318)	p Value
Age, mean ± SD, y	63 .7 ± 5.3	61.2 ± 5.0	<0.001
Sex, n (%)			0.45
Male	230 (56.4)	189 (59.4)	
Female	178 (43.6)	129 (40.6)	
Race, n (%)			0.03
White	385 (94.4)	286 (89.9)	
Black, Asian, other	23 (5.6)	32 (10.1)	
Ethnicity, n (%)			0.31
Hispanic or Latino	405 (98.4)	313 (99.3)	
Neither Hispanic nor Latino	3 (1.6)	5 (0.7)	
Smoking, n (%)			0.37
Current	221 (54.2)	161 (50.6)	
Former	187 (45.8)	157 (49.4)	
Pack-years smoked, mean ± SD			
Current smokers	64.8 ± 25.8	55.5 ± 20.9	<0.001
Former smokers	66.7 ± 30.6	55.2 ± 26.9	<0.001
Self-reported history of COPD, n (%)			
Yes	43 (10.5)	18 (5.7)	0.02
No	365 (89.5)	300 (94.3)	
FH of lung cancer, n (%)			0.08*
Yes	113 (28.9)	69 (22.8)	
No	278 (71.1)	233 (77.2)	
Missing	n=17	n=16	
Stage, n (%)			—
I	298 (73.0)	—	
II	29 (7.1)	—	
III	55 (13.5)	—	
IV	20 (5.0)	—	
Carcinoid, unknown	6 (1.5)	—	
Histologic subtype, n (%)			—
Adenocarcinoma	290 (71.1)	—	
Squamous cell carcinoma	81 (19.9)	—	
Other, NOS, unknown	37 (9.1)	—	

P Values calculated using Fisher's exact test for categorical variables, Student's t test for continuous variables.

* P value for family history of lung cancer was calculated without missing data.

Validation:

DECAMP-1 (see previous annual report for details): Access to this dataset was granted by the DECAMP biomarker committee and image transfer completed in March 2021. Due to issues with reorganization of research priorities at Mayo Clinic during the pandemic, only a subset of the DECAMP-1 dataset was ultimately analyzed. As previously reported, this dataset included 274 nodules (183 malignant and 91 benign, confirmed), yielded an AUC of 0.66 (strict validation) and 0.74 (loose validation).

a. Strict DECAMP-1 validation (i.e., using the 8-feature logistic model developed from the NLST data to impute the probability of lung cancer occurrence for each DECAMP case): AUC: 0.6567
b. Loose DECAMP-1 validation (i.e., using the same 8 features identified from the NLST data to then re-fit the logistic regression, plus Bootstrap correction): AUC: 0.7415

The following, alternative validation datasets were secured, curated and analyzed. *Note that no funding from this grant was used for these analyses*.

Lung Tissue Research Consortium validation (see previous annual report for details):

The radiomic model was validated using the Lung Tissue Research Consortium dataset, comprised of 88 benign and 89 malignant nodules. This cohort was considered "high-risk" as all nodules in this cohort were evaluated by expert radiologists and felt to be suspicious enough for malignancy to require surgical resection (i.e. a nodules, benign and malignant, were resected lung nodules and therefore with a high pre-test probability than typical screen- or incidentally identified lung nodules). Using these 177 nodules, the results were as follow: Sensitivity: 87.6%, Specificity: 68.2%, positive predictive value: 73.6%, negative predictive value: 84.5%. Negative likelihood ratio was 0.18 (95% CI 0.10-0.32) and positive likelihood ratio 5.51 (95% CI 3.11-9.77).

Vanderbilt nodule cohort validation (see previous annual report for details)

A total of 170 incidentally identified lung nodules from a well curated indeterminate pulmonary nodule registry database at Vanderbilt University, Nashville, TN, were used for independent external validation of the model described above. Cases were excluded due to missing slices, inability to segment or lack of sufficient information to calculate the Brock Score See flow chart below). The CT scans in DICOM format were transferred to Mayo Clinic Rochester, MN, for radiomic analysis.

Comparison of Classifier with Brock Model (for additional details see prior annual report)

The performance of the Brock model, a well validated nodule malignancy probability calculator widely used in clinical practice, developed from the Pan-Canadian Early Detection of Lung Cancer Study (Pan Can) was compared with our model in both the NLST LDCT and Vanderbilt incidentally detected nodule databases. Brock scores for 685 NLST nodules were calculated and compared with the prediction of our radiomic model by ROC analysis. In addition, comparative ROC analysis was performed on subsets of nodules classified based on pre-test malignancy probability as follows: low probability (Brock score <10%, N=350), intermediate probability (Brock score ≥10% but <60%, N=314) and high probability (Brock score ≥ 60%, N=21).

The Vanderbilt external validation set included 170 consecutive patients with incidentally identified IPNs (diameter 7-30 mm) enrolled into the Vanderbilt University pulmonary nodule registry. In the Vanderbilt University cohort, the mean diameter of the malignant nodules was larger than the benign nodules, 10.3 mm CI (9.4-11.3mm) versus 17.5 mm CI (16.2-17.8 mm), respectively ($p<0.001$).

Using the optimal cutoff of 0.478 identified via Youden's index, the sensitivity and specificity of the BRODERS classifier were 88.7% and 86.2% in the NLST screen-detected nodule cohort (n=685), respectively. For nodules with intermediate pre-test probability of malignancy (5-65%) by the Brock model (n=416) the Sensitivity was 91.9% and the Specificity was 71.6% using the same cutoff.

For the entire Vanderbilt incidental nodule dataset (n=170), the Sensitivity was 92.3%, the Specificity was 62.0%, the positive predictive value (PPV) was 73.7% and the negative predictive value (NPV) was 87.5%. For nodules with intermediate pre-test probability of malignancy by the Brock model (n=97), the Sensitivity was 94%, Specificity was 46%, the PPV was 78.4% and the NPV was 79.2%. \

The direct correlation between the Brock Model and the BRODERS classifier for the Vanderbilt University cohort are shown in **Figures 1 and 2** below, which show the ROC comparing Brock model versus BRODERS for the entire NLST (figure 1) and Vanderbilt (figure 2) cohorts, and subsets of the cohort classified as low and intermediate pre-test malignancy risk. In both cohorts the AUC are significantly greater for the BRODERS model compared to the Brock model at all pre-test malignancy probabilities ($P<0.001$). The difference is most pronounced in the intermediate pre-test malignancy risk group. The benign resection rates based on the hypothetical application of the BRODERS classifier to the NLST and the Vanderbilt datasets are 12% and 26% for the entire cohorts and 10% and 22% for the Brock model intermediate probability nodules (5-65%).

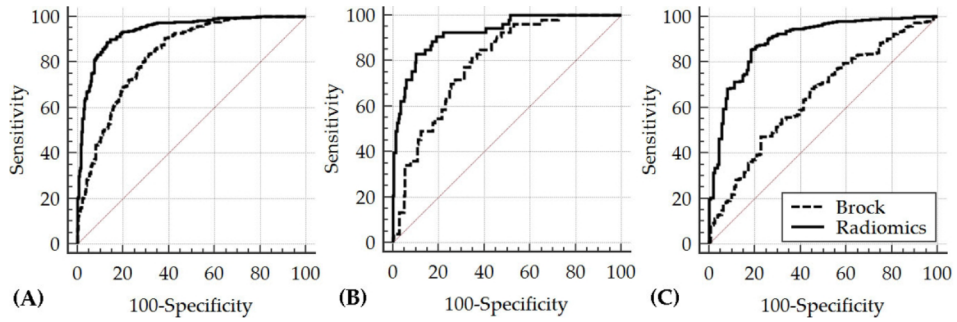

Figure 1. ROC for the NLST cohort comparing the Brock and Radiomics classifications. Panel (A) is for the entire cohort. AUC Brock 0.833 (95% CI = 0.803-0.860); AUC Radiomics 0.939 (0.918-0.955). Panel (B) is for the low risk (Brock score < 5%) group, AUC Brock 0.795 (0.74-0.842); AUC Radiomics 0.925 (0.886-0.954). Panel (C) is for the intermediate risk (5% ☐ Brock Score < 65%) group. AUC Brock 0.648 (0.599-0.694); AUC Radiomics 0.893 (0.859-0.922).

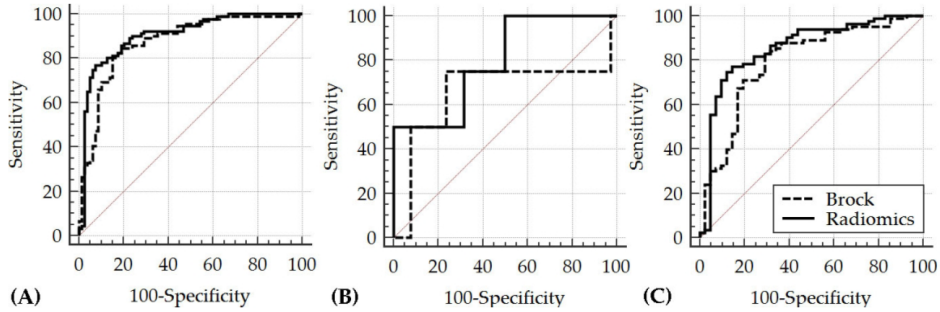

Figure 2. ROC for the Vanderbilt cohort comparing the Brock and Radiomics classifications. Panel (A) is for the entire cohort. AUC Brock 0.872 (95% CI = 0.812-0.918); AUC Radiomics 0.904 (0.849-0.943). Panel (B) is for the low risk (Brock score < 5%) group, AUC Brock 0.658 (0.496-0.797); AUC Radiomics 0.796 (0.644-0.904). Panel (C) is for the intermediate risk (5% ☐ Brock Score < 65) group. AUC Brock 0.798 (0.717-0.864); AUC Radiomics 0.856 (0.782-0.912).

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.

Nothing to report

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.

See prior reports.

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

Not applicable

4. **IMPACT:** D*escribe 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:*

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 disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

One of the main obstacle to implementing lung cancer screening has been the large number of individuals with false positive screening CTs (approximately 40% in the NLST), which is likely to result in unnecessary invasive diagnostic interventions with excessive morbidity, mortality, patient stress and healthcare expenses, particularly in individuals with lung nodules with intermediate pretest probability of malignancy.

We have previously demonstrated that volumetric CT-based quantitative characterization can risk-stratify lung nodules of the adenocarcinoma spectrum. This approach eliminates the intra- and inter-observer variability and subjectivity of CT image interpretation by trained radiologists. In addition, modern digital CT images include a large amount of valuable high-dimensional data not currently utilized to assist in diagnosis. We used to the NLST dataset to develop and internally validate a radiological multivariate model that include quantitative radiological features distinguishing malignant from benign CT-screen detected indeterminate pulmonary nodules. Initial validation of this model in independent cohorts has been promising and suggests that a significant number of individuals with lung nodules could be spared additional non-invasive and invasive diagnostic interventions, mitigating the risk of unnecessary procedures associated with morbidity, mortality and healthcare costs. In addition, this tool leverages available data that are currently not exploited by clinicians and radiologists, obviating the need for further interventions, as required by other currently assessed biomarkers. This could lead to substantial improvement in lung nodule management, if available to a large audience of clinicians and radiologists as a software-based image analytical tool which could substantially reduce error and reduce the risk of unnecessary invasive and non-invasive procedures.

We plan to implement BRODERS at both Mayo Clinic and Vanderbilt University for research purposes and in an ongoing collaborative effort plan to pursue FDA 510(k) clearance as a joint Mayo Clinic – Vanderbilt University collaboration.

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.*

Our project, if successful could have a major impact on lung nodule management, by offering clinicians and radiologists reproducible tools to assist in the management of incidentally or screen-identified lung nodules, a major healthcare problem that affects Veteran and non-Veteran populations. Quantitative nodule analysis can be applied to existing CT scans obtained for screening or clinical indications and do not require additional testing beyond software application of image analytics. Our quantitative analytics tool could help standardize the management of lung nodules and lead to a substantial reduction in the unnecessary morbidity, mortality and healthcare costs.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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:*

There has not been a major change in our approach, except for the pursuit of additional validation datasets given the considerable delays in accumulating enough cases in the DECAMP1 dataset to allow for enough power. None of the Department of Defense funds allocated to these analyses.

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.

This award was effective on September 30, 2015, but because of the relocation of the grant PI (Fabien Maldonado) from Mayo Clinic, Rochester, MN to Vanderbilt University, Nashville, TN, substantial delays were incurred from the need to establish subcontracts between the three partnering institutions (Mayo Clinic, Brown University and Vanderbilt University), which were eventually finalized in April 2016. This resulted in a significant delay for case selection and image transfer from the ACRIN and LSS core labs and our work on the development and optimization of discriminative radiological quantitative variables.

However, the variables were developed and optimized by the end of 2016 and both model 1 (radiological model) and model 2 (clinical-radiological model) were developed and internally validated using LASSO for variable penalization and selection and bootstrapping for internal validation. External validation, however, has been hampered by delays in recruitment in our planned validation dataset, the DECAMP1 dataset (PI: Dr. Avrum Spira). Accordingly, we have pursued additional validation cohorts and were able to validate our radiological model using the LTRC and Vanderbilt datasets.

Two unexpected major events prevented us from completing this work in the past 2 years and motivated a request for a no-cost extension: (1) the COVID-19 pandemic, which placed a disproportionate burden on our division of pulmonary and critical medicine and slowed down our work considerably, and (2) the sudden and unexpected passing of Pierre Massion, MD, on April 4th, 2021, who led the Massion Biomarker Laboratory at Vanderbilt University Medical Center, in which image analysis was to be performed, required us to modify our plans and transfer the images to the Biomedical Imaging Resource laboratory at Mayo Clinic, Rochester, MN, for further image segmentation and analysis. These datasets have now been successfully transferred.

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.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. 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).*

Journal publication:
Peikert T, Duan F, Rajagopalan S, Karwoski RA, Clay R, Robb RA, Qin Z, Sicks J, Bartholmai BJ, Maldonado F. Novel high-resolution computed tomography-based radiomic classifier for screen-identified pulmonary nodules in the National Lung Screening Trial. PLoS One. 2018 May 14;13(5):e0196910. Maldonado F, Varghese C, Rajagopalan S, Duan F, Balar A, Lakhani D, Antic S, Massion PP, Johnson T, Karwoski,R, Robb R, Bartholmai B, Peikert T. Validation of the BRODERS classifier (Benign VS. aggressive nOdule Evaluation using Radiomic Stratification), a novel high-resolution computed tomography-based radiomic classifier for indeterminate pulmonary nodules. European Respiratory Journal (published April 1, 2021)

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).*

Nothing to report

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.*

Conference paper:

Computed tomography-based radiomic classifier distinguishes malignant from benign nodules in the national screening trial
18th World Conference on Lung Cancer
October 15 - 18 2017 | Yokohama, Japan http://wclc2017.iaslc.org/
Computed tomography-based radiomic classifier distinguishes malignant from benign nodules in the national screening trial

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.

Nothing to report

Technologies or techniques

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Novel CT-based quantitative analytics to distinguish benign from malignant nodules. How this novel analytical tool will be shared has not yet been determined.

Inventions, patent applications, and/or licenses

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. 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.

SYSTEM AND METHOD FOR TOMOGRAPHY-BASED RADIOMIC MASS ANALYSIS

Publication number: 20190125279

Abstract: Systems and methods are provided for classifying a tissue mass as malignant or benign. The method includes identifying a region of interest in the tissue mass in computed tomography (CT) imaging data, segmenting the CT imaging data to delimit at least a portio of the tissue mass into image segments, extracting a set of radiomic parameters indicative o the tissue mass. The set of radiomic parameters may include tissue mass location, tissue ma shape, tissue mass surface characteristic, or tissue mass texture distribution indicative of th amount of image segments identified.

Type: Application

Filed: October 16, 2018

Publication date: May 2, 2019

Inventors: Tobias Peikert, Ronald A. Karwoski, Fabien Maldonado, Srinivasan Rajagopalan, Brian J. Bartholmai

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;*
- *physical 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

What individuals have worked on the project?

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). 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 Ford Foundation (Complete only if the funding support is provided from other than this award.)*

NOTHING TO REPORT

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.

Nothing to report

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:
<u>Organization Name:</u>
<u>Location of Organization: (if foreign location list country)</u>
<u>Partner's contribution to the project</u> (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.*

NOTHING TO REPORT

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

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 applications, study questionnaires, and surveys, etc.*