AWARD NUMBER: W81XWH-15-1-0110

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

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REPORT DATE: October 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Annual	09/30/2018 – 09/29/2019

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0110

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The widespread implementation of lung cancer screening, following favorable results of the National Lung Screening Trial (NLST) and more recently the European NELSON trial, will likely continue to exacerbate the widespread clinical problem of indeterminate pulmonary nodules, which were detected in 40% of high-risk individuals screened by low dose high-resolution computed tomography (HRCT) in the NLST. Because 96% of these nodules were benign, the issue of diagnostic resolution of incidentally and screen-identified lung nodules will become increasingly important. Current clinical and radiological risk prediction models, which allow risk-stratification of patients and individualize management of pulmonary nodules, are commonly used, but remain suboptimal, and optimization of the clinical management of larger (≥ 7 mm) screen-detected nodules is urgently needed to avoid unnecessary diagnostic interventions leading to unwarranted mortality, morbidity and healthcare costs. In our project, we explore the utility of a conventional radiomic approach to the classification of screen-detected indeterminate nodules, leveraging unexploited large datasets contained on digital HRCT images to estimate the probability of malignancy based on selected predictive quantitative radiologic features.

15. SUBJECT TERMS
Lung adenocarcinoma, Radiomics, Lung cancer screening, Chest computed tomography, Biomarkers, Lung nodules.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	20	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Lung cancer continues to account for more cancer-related mortality than the breast, prostate and colon cancer combined, and greater than half of lung cancer cases are still 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) can reduce mortality in high risk patients. Implementation of LDCT screening has however been challenging. A main reason for the low uptake of LDCT screening is the high false positive rate, and the uncertainty about optimal interval between screening rounds and cost-effectiveness. The high false positive rates noted in NLST has been improved by the application of the Lung Imaging Reporting and Data System (Lung-RADS) criteria, where smaller and part-solid nodules (<6mm), nodules with specific calcification patterns, perifissural nodules (<10 mm) are classified as benign. While Lung-RADS reduces the false positive rate to 5.3%, it also reduces sensitivity at baseline by about 10%. To put things in context, even applying the Lung-RADS criteria to 1000 patients in NLST, in an effort to prevent 3 cancer related deaths, 779 would have had normal scans, 180 who do not have cancer would have gotten an extra scan and 13 of those would have needed an unnecessary invasive procedure. This problem is compounded by the fat that incidentally identified lung nodules are also on the rise, presumably due to increased use of high-resolution CT (HRCT). Based on data from 2006 to 2012, it is estimated that around 1.5 million adult Americans will have a pulmonary nodule identified each year, which is almost certainly an underestimate. Because the vast majority of these incidentally- or screen-identified lung nodules will ultimately prove benign, efficient diagnostic investigations will be increasingly important and while many biomarkers are currently being evaluated to optimize nodule management, none has been widely adopted in clinical practice. Risk-stratification of nodules as allowed by current clinical prediction models remain suboptimal, and the development and validation of cost-effective tools to guide management of larger (≥ 7 mm) screen-detected nodules is needed to mitigate the problem of unnecessary diagnostic interventions leading to excessive mortality, morbidity and healthcare costs.

Quantitative radiologic analysis of available CT datasets using artificial intelligence (radiomics) is an attractive option, leveraging existing datasets, obviating the need for additional invasive or non-invasive investigations. Most recent approaches have focused on deep learning methods, which have shown promises in many other fields, with the caveat that predictive variables thus identified are without clear correlation to tumor biology, and that deep learning methods require large datasets for development and validation which are not easily accessible. In addition, there is great variability in image acquisition, feature extraction and statistical analysis of the various radiomics models described in literature. While many promising models have been developed, external validations are rare, a consequence of the paucity of available curated datasets and the risk of overfitting that continues to plague radiomic models, particularly those relying on deep-learning methods. It is also often unclear whether such models outperform validated simpler and readily accessible clinical prediction models.

We have previously described the development of a radiomic classifier that effectively distinguishes benign from malignant nodules using a training set of 726 indeterminate nodules from the NLST database, which was validated with relatively good diagnostic test performance on two independent datasets with large prevalence of malignancy (the available DECAMP1 dataset (currently still accruing) and the Lung Tissue Registry Consortium dataset with acceptable performance (0.66 and 0.80 AUC, respectively)). In the past year, we validated our model using a curated independent dataset from the Vanderbilt University lung nodule registry, and used clinical and radiologic variables to calculate the probability of malignancy of the NLST and Vanderbilt University registry datasets based on a commonly used and validated clinical

prediction rule, the Brock model, in order to estimate the probability of reclassification of screen- or incidentally-identified lung nodules with intermediate probability of malignancy (defined as 10% to 60% as calculated by a validated predictive model, the Brock model) into classes of low- or high-probability of malignancy.

2. KEYWORDS:

Lung adenocarcinoma, Radiomics, Lung cancer screening, Chest computed tomography, Biomarkers, Lung nodules.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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).

   Note that subcontracts with Brown University and Mayo Clinic (required due to relocation of the PI, Fabien Maldonado, to Vanderbilt University) were not established until March 2016 and as such work could not be started before that time.

   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. 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.

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

1. Milestone: Validation of a radiologic and combined clinical/radiologic prediction models (**Year 2 of the grant**).

   Enrollment for the DECAMP1 study continues to be considerably delayed. Completion of enrollment in the study was anticipated by December 2015 at the time of our application (August 2014), as 125 of the planned 500 patients had already been enrolled (see

attached original support letter from DECAMP1 PI Dr. Avrum Spira, Boston University). As of August 28, 2019: 383 nodules have been adjudicated, including 205 malignant and 133 benign nodules. Completion of accrual and adjudication is expected in the 2nd quarter of 2020 (PR. Avrum Spira, personal communication). As previously reported, an interim blind analysis of this dataset that included 274 nodules (183 malignant and 91 benign, confirmed) and using our radiologic model yielded an AUC of 0.66 (strict validation) and 0.74 (loose validation). These disappointing results were felt to be due to the very large number of malignant nodules in this cohort, likely to result to early adjudication of the most suspicious lung nodules.

We were however able to 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 103 malignant lung nodules and 99 benign lung nodules, as well as (2) the lung nodule cohort from the Lung Tissue Research Consortium, comprised of 88 benign and 89 malignant nodules. Similar to the early DECAMP-1 cohort, this 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). Note that funds from the award were not used for these external validation sets. The validation from the LTRC dataset was reported in a previous report and is summarized below. The current report will focus on updated analyses of the curated Vanderbilt dataset. A no -cost extension for the grant has been requested for final analysis of the DECAMP-1 cases expected in 2020.

What was accomplished under these goals?

a. Major activities

Summary of activities that occurred during the first year of the grant:

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, as below:

1. Bulk metrics based on the global shape descriptors of the nodule.
2. Intensity metrics based on the CT Hounsfield units within the nodule.
3. Metrics capturing the spatial location of the nodule.
4. Nodule texture metrics based on the texture exemplar distributions within the nodule.
5. Surround texture metrics based on the parenchymal texture exemplar distributions within a region surrounding the nodule.
6. Metrics capturing the surface descriptors of the nodule.
7. Metrics capturing the distribution of the surface exemplars of the nodule.

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

Multivariate analysis was performed using least absolute shrinkage and selection operator (LASSO) method for both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the multivariate statistical model. 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 as follows:

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.

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).

Validation:

1. DECAMP-1 (see previous report for details):

Due to considerable delay in enrollment of the DECAMP1 study (see above), validation of our model on a prospective cohort of screened individuals similar to those enrolled in the NLST is still pending. Application to access this dataset was completed and submitted to and approved by the DECAMP biomarker committee for image transfer. The most recent status update from DECAMP1 as of September 9, 2018 is as follow: Final accrual anticipated early 2020, current status as of 8/28/2019, 383 nodules have been adjudicated, including 205 malignant and 133 benign nodules. As previously reported, an interim analysis that 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

As we are awaiting full recruitment and adjudication of the DECAMP1 dataset, alternative validation datasets were pursued, curated and analyzed. *Note that no funding from this grant was used for these analyses*.

2. Lung Tissue Research Consortium validation (see previous 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%

PPV: 73.6%

NPV: 84.5%

Negative likelihood ratio 0.18 (95% CI 0.10-0.32)

Positive likelihood ratio 5.51 (95% CI 3.11-9.77)

While the results are clearly inferior to those expected based on our internal validation, the nature of the LTRC database comprised of nodules with a very high pretest probability of malignancy make these results encouraging as we are in the process of validating these results on the more similar Vanderbilt and DECAMP1 database.

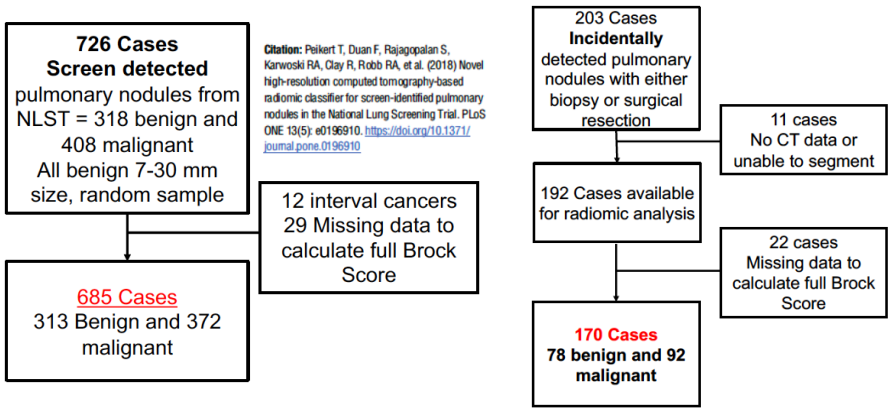
Year 3: Vanderbilt nodule cohort validation

Two hundred and three incidentally identified lung nodules, in 203 patients, from a well curated indeterminate pulmonary nodule registry database at Vanderbilt University, Nashville, TN, was 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. All the investigators from Mayo Clinic (C.V., S.R., R.K., B.B, and T.P.) were blinded to the clinical information available for each patient, including baseline patient information (demographics, smoking status, prior cancer history), pathological information (histopathological type, staging) and long term outcomes (death, alive with or without evidence of disease). Semi-automated segmentation was performed by the ANALYZE software as previously described. The radiomics classifier was then used to predict the malignancy risk of the nodules.

Comparison of Classifier with Brock Model

The performance of Brock, 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 was calculated, with the exclusion of cases in which an interval cancer developed during the screening period (n=12) and those that did not have values in the NLST curation necessary for Brock calculation (n=29), see flow chart below. Brock model prediction on this cohort was 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 $\geq$10% but <60%, N=314) and high probability (Brock score $\geq$ 60%, N=21). Similar comparisons of Brock and our classifier was

performed on the incidentally discovered Vanderbilt nodules. (SAS Institute Inc., Cary, NC, 1989-2019) was used for statistical analysis.



Flow charts: Nodule selection for radiomic analysis and Brock score calculation (left: NLST, right: Vanderbilt.

Validation data:

Table 1 shows the baseline characteristics of the patients in the NLST cohort in comparison with the Vanderbilt cohort. Although the distribution of malignant versus benign nodules is similar in both cohorts, many of the other baseline characteristics including smoking status, nodule size and speculation is different between the two groups, as would be expected in comparing a screen-detected nodule cohort with a incidentally discovered nodule cohort. **Tables 2 and 3** show the distribution of malignancies and their radiomics classifications at various Brock score categories

Figures 4 and 5 compare histology (ground truth) versus radiomics and corresponding Brock scores. In the NLST screen detected nodule cohort, the positive predictive value (PPV) of radiomics is 88.5% and the negative predictive value (NPV) is 86.5%. At low pre-test cancer risk the PPV of radiomics is 80% and NPV is 89.2%, whereas for intermediate risk the PPV is 90.9% and NPV is 75.8%.

For the entire Vanderbilt incidental nodule cohort the positive predictive value (PPV) is 73.7% and negative predictive value is 87.5%. At low pre-test cancer risk the PPV of radiomics is 37% and the NPV is 92.9%, whereas for intermediate risk the PPV is 84.3% and the NPV is 71.4%. In summary as the pre-malignancy risk increases the PPV of our tool increases substantially while the NPV does not decrease substantially.

Figures 6 and 7 show the receiver operator characteristic curves (ROC) comparing Brock score versus radiomics for the entire NLST cohort, and subsets of the cohort classified as intermediate pre-test malignancy risk. **Figures 8 and 9** shows the ROC for the Vanderbilt cohort similarly classified. In both cohorts the area under the cure (AUC) are significantly greater in the radiomics model compared to the Brock model at all pre-test malignancy probabilities. The difference is most pronounced in the intermediate pre-test malignancy risk group. Which suggests that our radiomic model may help reclassify a significant number of lung nodules with intermediate pre-test probability of malignancy

Table 1:

	NLST (n=685)	Vanderbilt (n=170)
Age mean years [SD]	63 [5.3]	66 [7.6]
Gender [%]		
Men	392 [57.2]	113 [66.5]
Women	293 [42.8]	57 [33.5]
Race		
Caucasian	632 [92.3]	152 [89.4]
Black, Asian, other	53 [7.7]	18 [10.6]
Smoking [%]		
Current	362 [52.8]	108 [64]
Former	327 [47.2]	58 [34]
Never	0	4 [2]
Smoking pack years mean [SD]	61 [27.1]	57 [34.2]
Mode of Nodule detection	Screening	Incidental
Nodule Diagnosis [%]		
Benign	313 [55.7]	78 [46]
Malignant	372 [54.3]	92 [54]
Nodule Size mean mm [SD]	12.2 [6.5]	14.6 [6.9]
Spiculation [%]	199 [29.1]	20 [11.8]

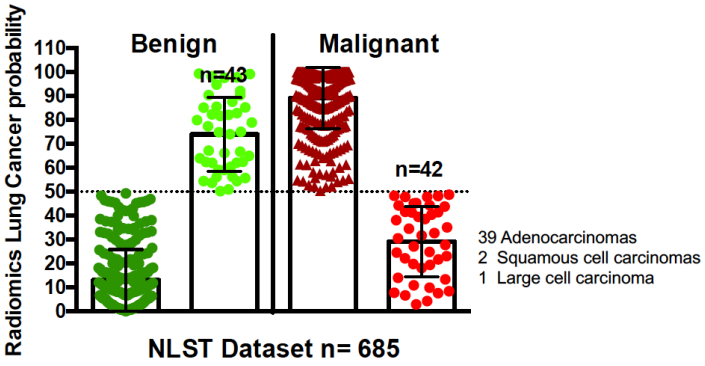
Table 2: Types of malignancies in the NLST cohort (B: Brock Score, R_Benign: Benign classification by radiomics, R_Malignant: Malignant classification by radiomics)

Histology	B < 10	10 < B < 60	B > 60	R_Benign	R_Malignant
Adnenocarcinoma (N=268)	73	178	17	39	229
Squamous Cell (N=71)	23	44	4	2	69
Large Cell (N=18)	6	12	0	1	17
Small Cell (N=11)	3	8	0	0	11
Carcinoid (N=4)	2	2	0	0	4

Table 3: Types of malignancies in the Vanderbilt cohort (B: Brock Score, R_Benign: Benign classification by radiomics, R Malignant: Malignant classification by radiomics)

Histology	B < 10	10 < B < 60	B > 60	R_Benign	R_Malignant
Adnenocarcinoma (N=60)	7	51	2	3	57
Squamous Cell (N=24)	5	17	2	2	22
Large Cell (N=3)	0	3	0	0	3
Small Cell (N=3)	0	3	0	1	2
Carcinoid (N=1)	1	0	0	1	0

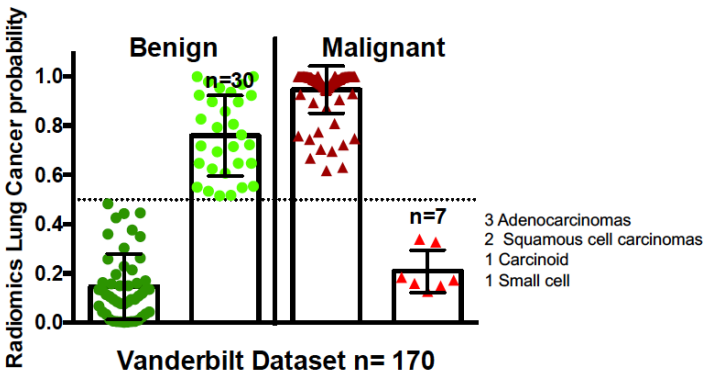
Figure 4: Histology (ground truth) versus radiomics and corresponding Brock scores for the NLST dataset:



	Histology	Radiomics Benign	Radiomics Malignant
Benign	313	270	43
Malignant	372	42	330

11.5% predicted benign resections

Figure 5: Histology (ground truth) versus radiomics and corresponding Brock scores for the Vanderbilt dataset:



	Histology	Radiomics Benign	Radiomics Malignant
Benign	79	49	30
Malignant	91	7	84

26% predicted benign resections

Figure 6: ROC for the entire NLST cohort. AUC Brock is 0.83 (95% CI=0.80-0.86). AUC Radiomics is 0.94 (95% CI=0.92-0.96)

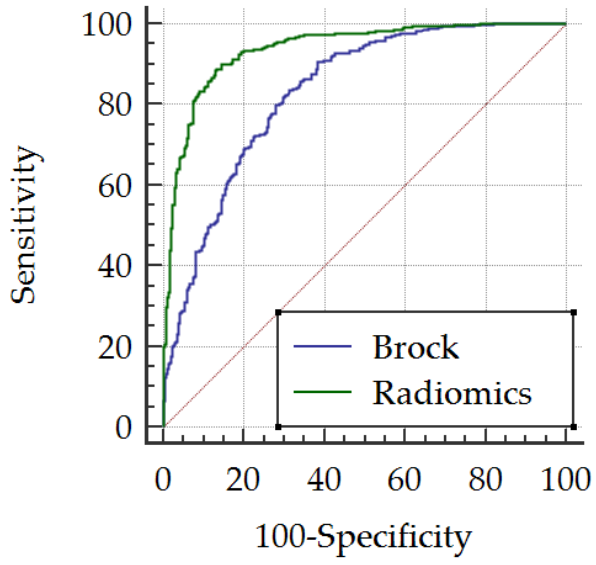


Figure 7: ROC for intermediate risk (10≤Brock <60%) NLST subgroup. AUC Brock is 0.61 (95% CI=0.55-0.66). AUC Radiomics is 0.88 (95% CI=0.84-0.92)

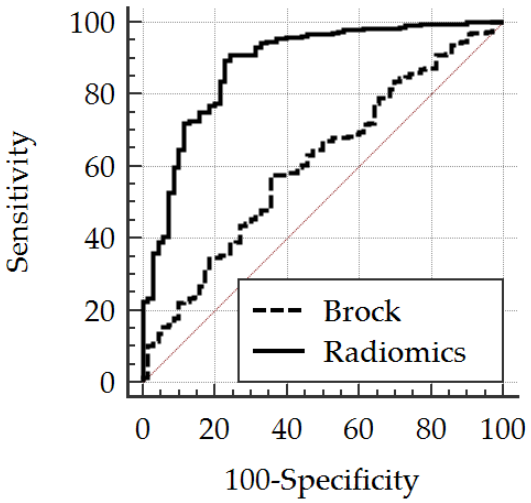


Figure 8: ROC for the entire Vanderbilt cohort. AUC Brock is 0.87 (95% CI=0.81-0.92). AUC Radiomics is 0.90 (95% CI=0.85-0.94)

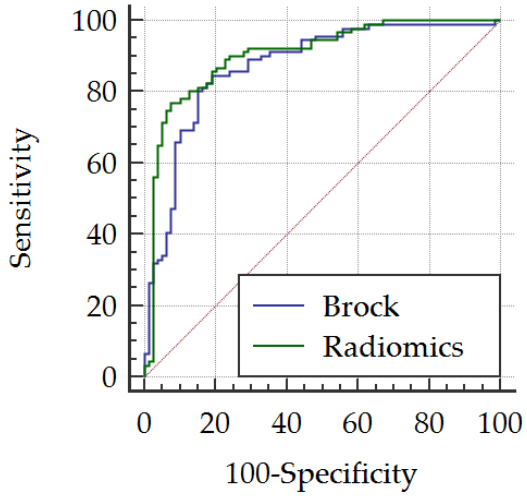
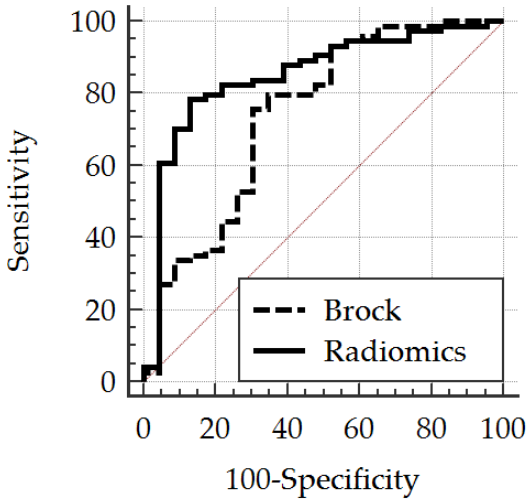


Figure 9: ROC for intermediate risk (10≤Brock <60%) Vanderbilt subgroup. AUC Brock is 0.74 (95% CI=0.64-0.83). AUC Radiomics is 0.85 (95% CI=0.76-0.92)



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 these goals?

As described in our the initial proposal, we are still planning on validating our promising results on the DECAMP-1 dataset, which we expect to be available in 2020. We have requested another no-cost extension for that purpose. One the data are available, remaining CT datasets will be transferred to Mayo Clinic and analyzed in a blinded fashion, an results of radiomic analyses will then be transferred to Brown University for final analysis. Pending continued favorable results, w hop to integrate this technology in a prospective study evaluating the impact of this novel radiomic biomarker on patient care in terms of clinical outcomes, morbidity, mortality, healthcare costs and pursue an FDA approval pathway.

4. IMPACT

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

An estimated 1.5 million new lung nodules are identified via chest CT annually in the US, which is likely an underestimate given the ever-expanding use of HRCT in the US and in the world. This is also likely to increase markedly with implementation of lung cancer screening for high-risk individuals, with a number of individuals eligible for lung cancer screening estimated around 10 million in the US alone. In 2015, out of 8.6 million US individuals eligible for lung cancer screening as per NLST eligibility criteria, only 250,000 were screened, resulting in an estimated 750 lung cancer-related deaths averted, as opposed to the estimated 12,500 lives that could be saved with full implementation of lung cancer screening. 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), 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.

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?

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

Changes in approach and reasons for change:

There has not been a major change in approach, except for the pursuit of additional validation sets 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. We are awaiting the DECAMP1 final results.

Actual or anticipated problems or delays 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.

Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing to report

6. PRODUCTS

Publications, conference papers, and presentations

1. 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
2. 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.

Website(s) or other internet site(s):

Nothing to report

Technologies or techniques:

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:

Nothing to report

Other products:

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Tobias Peikert
Project Role: PD/PI
Research Identifier: N/A
Nearest Person Months: 0.0
Contribution to the Project: Mayo Clinic PI, administrative leadership at Mayo Clinic, review and selection of all benign NLST (nodules) training set and benign and malignant DECAMP nodules. Shared supervision of Dr. Rajagopalan and Ron Karwoski with Dr. Bartholmai. Participation in weekly team videoconferences.

Name: Srinivasan Rajagopalan
Project Role: Co-Investigator
Research Identifier: 0000-0003-3286-1529
Nearest Person Months: 0.0
Contribution to the Project: Image analysis and development of imaging variables. Participation in weekly meetings.

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

Fabien Maldonado, M.D.

Active Support

W81XWH-15-1-0110 (Maldonado)	09/30/15 – 09/29/19	0.00 calendar months
Department of Defense	$176,102 (NCE)	

"Noninvasive Characterization of Indeterminate Pulmonary Nodules Detected on Chest High-Resolution Computed Tomography"
Specific Aims: 1) to develop an imaging-based approach including HRCT lesion density, quantitative texture analysis of the lesion surrounding local, lobar and whole lung lung-parenchyma, lesion shape, size and location; 2) to develop a combined radiological-clinical risk model to distinguish benign from malignant lung nodules based on NLST data and compare the performance of this model to the radiological model developed in Aim 1.

W81XWH-17-1-0442 (Blackwell)	09/30/17 – 09/29/20	0.30 calendar months
Department of Defense	$419,344	

"Herpesviruses and Immune Dyregulation in Pulmonary Fibrosis"

These proposed studies will show whether anti-herpesvirus immune responses can serve as prognostic biomarkers in IPF and identify IPF patients who could benefit from targeted anti-viral therapies.

5 U01 CA196405-05 (Massion) 09/24/15 – 08/31/20 1.20 calendar months
NIH/NHLBI $979,812
"Cellular, Molecular, and Quantitative Imaging"
With implementation of screening programs for lung cancer, we are facing challenges related to overdiagnosis and overtreatment of indolent lung adenocarcinomas (ADC). Our project will improve prediction models by integrating quantitative imaging, molecular and cellular determinants to be paradigm-shifting in the clinical management of patients with early ADC.

1 R01 EB 024864-02 (Alterovitz) 09/15/17 – 06/30/21 0.12 calendar months
NIH/NIBIB $6,214
"Bronchoscopic Steerable Needles for Transparenchymal Access to Lung Nodules"
The objective of this proposal is to create a new robotic system that deploys bronchoscopic steerable needles that can steer through the lung parenchyma to safely biopsy nodules that are currently inaccessible bronchoscopically. Dr. Maldonado will provide clinical advice to the team at Vanderbilt on robot design, workflow, biopsy collection, and other aspects of the system related to usability and functionality in the practical clinical environment.

1 R41 HL140709-01 (Hendrick) 05/01/19 – 11/30/19 0.36 calendar months
NIH/NHLBI $10,518
"Reopening the Central Airway with Needle-Size Tentacle Manipulators"
The major goal of this is to create a robot that can remove a central airway obstruction. Dr. Maldonado, will advise the PI on all clinical aspects of development and will guide the ultimate design of the robotic system from a usability and workflow perspective. Dr. Maldonado will also conduct many of the initial phantom and cadaver experiments and provide rapid clinical feedback for quick prototype iteration of the surgical robotic system.

Tobias Peikert, M.D.

ACTIVE

W81XWH-15-1-0110 (Maldonado) 09/30/15 – 09/29/19 0.0 calendar months
Department of Defense $67,755 (no cost extension)
"Noninvasive characterization of indeterminate pulmonary nodules detected on chest high-resolution computed tomography"
Specific Aims: 1) to develop an imaging-based approach including HRCT lesion density, quantitative texture analysis of the lesion surrounding local, lobar and whole lung lung-parenchyma, lesion shape, size and location; 2) to develop a combined radiological-clinical risk model to distinguish benign from malignant lung nodules based on NLST data and compare the performance of this model to the radiological model developed in Aim 1.

Schulze Foundation (Tobias Peikert) 06/01/14-05/31/20 0.12 calendar months
$213,839
"Anti-Tumor Immunity in Response to a Modified Vaccine Strain Measles Virus in MM".
Specific Aims: Support the conduct and correlative studies of MC1023 including a maximal dose extension cohort (20 patients total). Explore possible synergistic effects between MV-

NIS and FAP-CAR T-cells in animal models.

Career Development Award (Peikert) 05/01/16-10/30/19 0.96 calendar months
Walter & Leonore Annenberg $38,461
"Therapeutic Strategies using the Modified Vaccine Strain Measles Virus (MV-NIS) in Malignant Mesothelioma". Specific Aims: 1) To conduct maximal tolerated dose (MTD) expansion cohort study to explore the clinical effects on overall survival for the intrapleural administration of MV-NIS in MM. 2) To conduct correlative studies to investigate replication and shedding of MV-NIS, and viral effects on local and systemic innate and adaptive anti-viral and anti-tumor immunity. 3) To evaluate the value of combination therapy of MV-NIS with CAR T- Cells and Anti-PD1/PD-L1 targeted therapies

Mayo Clinic Development (Peikert) 02/25/19-11/30/19 1.56 calendar months
SEAFAM Award $313,808
"Phase I/II Study Investigating the Intrapleural Administration of Measles Virus-Infected Natural Killer Cells (MV-NK) in Patients with Malignant Pleural Effusions"
Specific Aims: 1) Successfully submit and obtain IND to investigate the safety and efficiency of the intrapleural administration of MV-infected NK-cells in patients with malignant pleural effusions (including MPM) in a Phase I/II study with safety run in starting at the end of 2019.

NCI (Peikert and Bartholmai) 07/01/19-06/30/20 1.20 calendar months
$190,604
"Proposal to perform radiology reads and quantitative analysis of CT images"
Specific Aims: Perform radiological interpretation and quantitative CT analysis for chest imaging studies collected as part of the NCI-Sherlock Study.

Srinivasan Rajagopalan, Ph.D.

ACTIVE
W81XWH-15-1-0110 (Maldonado) 09/30/15 – 09/29/19 0.0 calendar months
Department of Defense $67,755 (no cost extension)
"Noninvasive characterization of indeterminate pulmonary nodules detected on chest high-resolution computed tomography"
Specific Aims: 1) to develop an imaging-based approach including HRCT lesion density, quantitative texture analysis of the lesion surrounding local, lobar and whole lung lung-parenchyma, lesion shape, size and location; 2) to develop a combined radiological-clinical risk model to distinguish benign from malignant lung nodules based on NLST data and compare the performance of this model to the radiological model developed in Aim 1.

What other organizations were involved as partners?
Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

None.