Moffitt Imaging Biomarker VAlidation Center (MIBVAC)

Quantitative Imaging and Radiomics in the Early Detection of Lung Cancer

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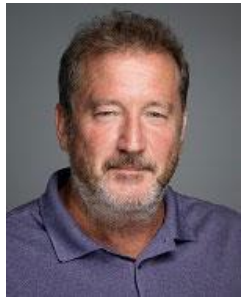
Departments of
Cancer Physiology and
Radiology



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Department of Biostatistics
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Moffitt Imaging Biomarker VAlidation Center (MIBVAC)

- **Aim 1. Breast Cancer**
- **Aim 2. Lung Cancer**
  - 2a. Establish retrospective lung cancer screening (LCS) and incidental pulmonary nodule (IPN) datasets to develop and validate clinical-radiomic models for risk assessment, diagnostic discrimination, overdiagnosis, and prognosis;
  - 2b. Establish prospective LCS and IPN cohorts, with real-time data curation, feature extraction, and biospecimen collection, for further clinical-radiomic model development and validation
- **Core & Supplemental Funds. Prostate Cancer**
- **Other Areas (non-funded): Sarcoma, Cervical, Brain, Liver, Pancreatic**

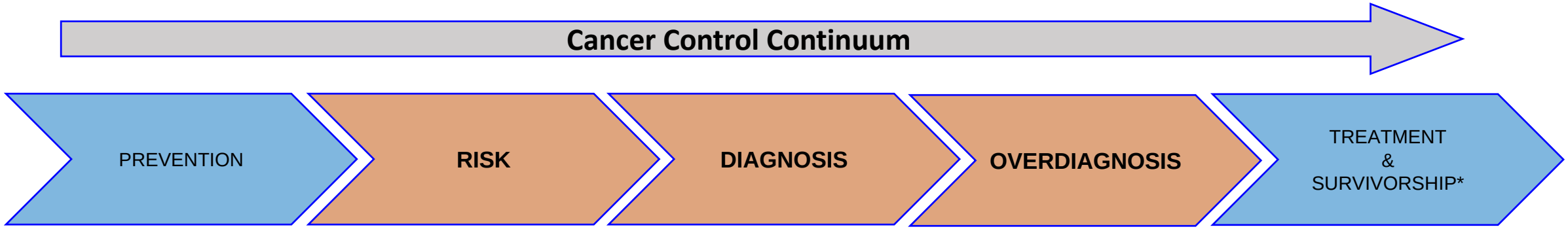
I. Summary of Progress for Aim 2

- 25+ publications directly or partially related
  - Collaborations with Vanderbilt (Pierre Massion), UCLA (Deni Aberle), USF (Hall and Goldgof)
- Curated retrospective LCS and IPNs cohorts and established prospective observational trials for LCS and IPNs
- Expanded LCS prospective recruitment to Millennium Physician Group, Port Charlotte County, FL
- Consenting patients for lung team project team 2 (LTP2)
- Developed new radiomics and analytic pipelines
  - Decision tree analyses, Machine Learning, Deep Learning, Ensembles

Lung Cancer Imaging Repository

- **NLST (N > 1000 patients w/ multiple time-points and images/per patient)**
- **Prospective cohorts for LCS (N = 500+) and IPNs (N = 200+)**
  - Images, risk factor data, blood, nasal swabs, oral gargle, spirometry
- **Expanded LCS recruitment to Millennium Physician Group: 50 prospective & 2,100 retrospective (>5000 images)**
  - Images and risk factor data
- **Retrospective IPN Cohort (N = 1000s [under development])**
  - Diagnostics
  - OS, PFS
- **Various lung cancer cohorts (>2400 pts)** ***– not funded by EDRN***
  - OS, PFS
  - TTR for surgically resected LC
  - Radiogenomics
- **Treatment: IO cohorts (N > 600 and growing), TKI cohorts (N = pending)** ***– not funded by EDRN***
  - OS, PFS, immune related adverse events, delta-radiomics

Radiomics the in Lung Cancer Control Continuum



- Identify which nodules will evolve and be diagnosed as cancer in the future
- Discriminate between benign and malignant nodules at the same time-point
- Predict behavior of a diagnosed lung cancer

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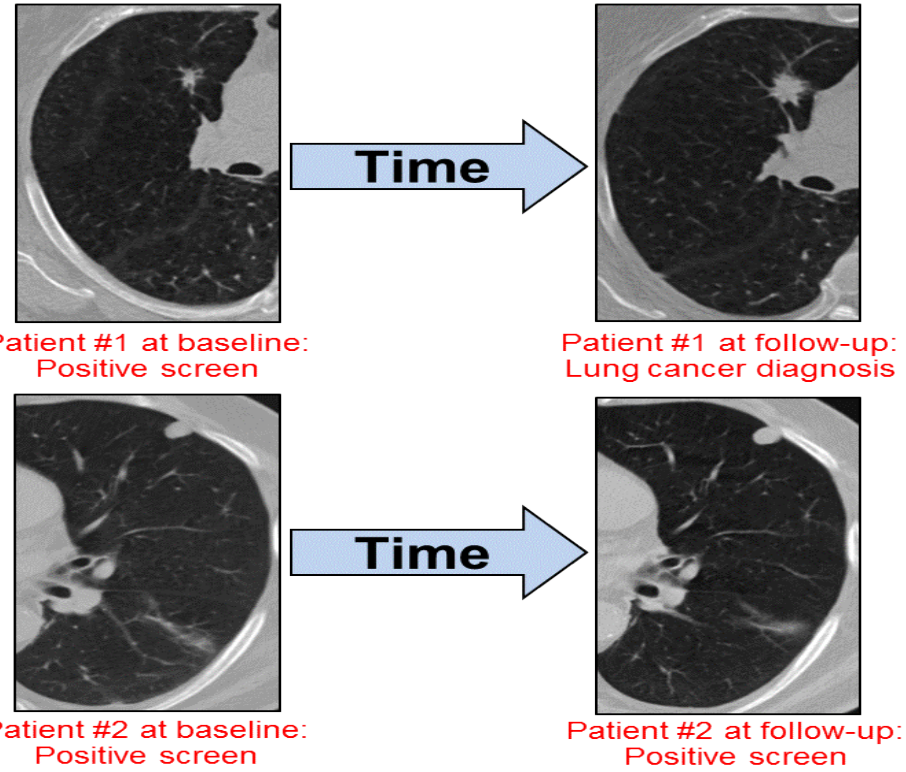
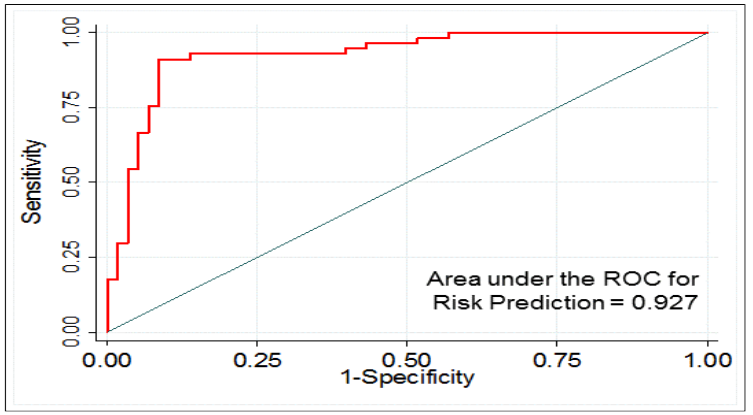
Risk Prediction Publications

Quantitative imaging features to predict future risk of cancer development





Risk Prediction Publications

ORIGINAL ARTICLE

Predicting Malignant Nodules from Screening CT Scans

Samuel Hawkins, MS,[a] Hua Wang, PhD,[b,c] Ying Liu, MD,[b,c] Alberto Garcia, AA,[c] Olya Stringfield, PhD,[c] Henry Krewer, BS,[a] Qian Li, MD,[b,c] Dmitry Cherezov, MS,[a] Robert A. Gatenby, MD,[d] Yoganand Balagurunathan, PhD,[c] Dmitry Goldgof, PhD,[a] Matthew B. Schabath, PhD,[e] Lawrence Hall, PhD,[a] Robert J. Gillies, PhD[c,d,*]

ORIGINAL RESEARCH

Delta radiomic features improve prediction for lung cancer incidence: A nested case–control analysis of the National L Screening Trial

Dmitry Cherezov[1] | Samuel H. Hawkins[2] | Dmitry B. Goldgof[1] | Lawrence O. Hall[1] | Ying Liu[2,3] | Qian Li[2,3] | Yoganand Balagurunathan[2] |

IEEE Access

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Delta Radiomics Improves Pulmonary Malignancy Prediction in Lung Cancer

ORIGINAL RESEARCH ■ THORACIC IMAGING

Radiologic Fe Pulmonary No Cancer Risk i Screening Tria Control Study[1]

Ying Liu, MD
Hua Wang, MD
Qian Li, MD
Melissa J. McGettigan, MD
Yoganand Balagurunathan, PhD
Alberto L. Garcia, BS
Zachary J. Thompson, PhD
John J. Heine, PhD
Zhaoxiang Ye, MD
Robert J. Gillies, PhD
Matthew B. Schabath, PhD

Personalized Medicine and Imaging

Clinical Cancer Research

Radiological Image Traits Predictive of Cancer Status in Pulmonary Nodules

Ying Liu[1,2], Yoganand Balagurunathan[2], Thomas Atwater[3], Sanja Antic[3], Qian Li[1,2], Ronald C. Walker[3,4,5], Gary T. Smith[4,5], Pierre P. Massion[3,4,5], Matthew B. Schabath[6], and Robert J. Gillies[2]

Abstract

Purpose: We propose a systematic methodology to quantify an area under the receiver operator characteristic curve (AUROC)

HHS Public Access

Author manuscript

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Conf Proc IEEE Int Conf Syst Man Cybern. 2016 October ; 2016: 001939–001944. doi:10.1109/SMC.2016.7844516

Improving malignancy prediction through feature selection informed by nodule size ranges in NLST

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hybrid models for lung nodule malignan prediction utilizing convolutional neura network ensembles and clinical data

Rahul Paul,[a] Matthew B. Schabath,[b] Robert Gillies,[c] Lawrence O. Hall,[a] and Dmitry B. Goldgof[a,*]

[a]University of South Florida, Department of Computer Science and Engi

Original Study

Comparison Between Radiol Features and Lung-RADS Malignancy of Screen-Detected the National Lung Scre

Qian Li,[1,2] Yoganand Balagurunathan,[2] Ying Liu,[1] Jin Qi, Matthew Zhaoxiang Ye,[1] Robert J. Gillies[2]

Abstract

In this study, we investigated the predictive value of radiological semantic features and l monary nodules malignancy risk at 3 screening rounds. We obtained 199 patients (139 nodule and 60 incident lung cancers) from the National Lung Screening Trial. It was found that outperformed lung-RADS at baseline and were comparable to lung-RADS at subsequer addition of semantic features to lung-RADS improves malignancy risk prediction.

Rationale: Lung computed tomography (CT) Screening Reporting and Data System (lung-RADS follow-up and management decisions in lung cancer screening. To date, little is known how lung-r compares with radiological semantic features in risk prediction and diagnostic discrimination. **Obje** the performance of radiological semantic features and lung-RADS in predicting nodule malign screening. **Methods:** We used data and low-dose CT (LDCT) images from the National Lung Scr The training cohort contained 60 patients with screen-detected incident lung cancers who had screen (T0) that was not diagnosed and then was diagnosed at second follow-up (T2), and controls who had 3 consecutive positive screens (T0 to T2) that were not diagnosed as lung cohort included 40 patients with incident lung cancers that were diagnosed at first follow-up positive controls. Twenty-four semantic features were scored on a point scale from the LDCT im linear predictor model was built on the semantic features and the performances were compared screening rounds. We also combined non–size-based semantic features with lung-RADS to i detection. **Results:** At T0, the average area under the receiver operating characteristic curve definition in risk prediction was 0.72. The average AUROC for contour at T1 in risk prediction a discrimination was 0.82 and 0.88, respectively. By comparison, the average AUROC of lung-RAD were 0.60, 0.76 and 0.87, respectively. The combined model of the semantic features and improvement with AUROCs of 0.74, 0.88 and 0.96 at T0, T1, and T2, respectively, achieved by addi (at T0) or contour (at T1 and T2). **Conclusion:** We find semantic features defined by border def performed similar to lung-RADS at follow-up time point and outperformed lung-RADS at baseline. These semantics alongside of lung-RADS shows improved performance to detect malignancy.

Clinical Lung Cancer, Vol. 19, No. 2, 148-56 © 2017 Elsevier Inc. All rights reserved.
Keywords: Lung cancer screening, Lung-RADS, NLST, Predictive, Semantic features

Journal of Medical Imaging

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Published online 2018 Mar 21. doi: 10.1117/1.JMI.5.1.011021 PMID: 29594181

Predicting malignant nodules by fusing deep features with classical radiomics features

Rahul Paul,[a] Samuel H. Hawkins,[a] Matthew B. Schabath,[b] Robert J. Gillies,[c] Lawrence O. Hall,[a] and Dmitry B. Goldgof[a,*]

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Abstract. Go to:

Lung cancer has a high incidence and mortality rate. Early detection and diagnosis of lung cancers is best achieved with low-dose computed tomography (CT). Classical radiomics features extracted from lung CT images have learning and for prognosis the transfer le Screening Tri versus positiv features and different colo features. A C NLST data, a obtained usin obtained usin

Keywords: transfer learn

1. Introdu

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Published in final edited form as:

Proc Int Jt Conf Neural Netw. 2018 July ; 2018: .

Predicting Nodule Malignancy using a CNN Ensemble Approach

Rahul Paul[a], **Lawrence Hall**[a], **Dmitry Goldgof**[a], **Matthew Schabath**[b], and **Robert Gillies**[c]

[a]Department of Computer Science and Engineering, University of South Florida, Tampa, Florida, USA

[b]Department of Cancer Epidemiology, H. L. Moffitt Cancer Center & Research Institute, Tampa, FL, USA

[c]Department of Cancer Imaging and Metabolism, H. L. Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Abstract

Lung cancer is the leading cause of cancer-related deaths globally, which makes early detection and diagnosis a high priority. Computed tomography (CT) is the method of choice for early detection and diagnosis of lung cancer. Radiomics features extracted from CT-detected lung nodules provide a good platform for early detection, diagnosis, and prognosis. In particular when using low dose CT for lung cancer screening, effective use of radiomics can yield a precise non-invasive approach to nodule tracking. Lately, with the advancement of deep learning, convolutional neural networks (CNN) are also being used to analyze lung nodules. In this study, our own trained CNNs, a pre-trained CNN and radiomics features were used for predictive analysis. Using subsets of participants from the National Lung Screening Trial, we investigated if the prediction of nodule malignancy could be further enhanced by an ensemble of classifiers using different feature sets and learning approaches. We extracted probability predictions from our different models on an unseen test set and combined them to generate better predictions. Ensembles were able to yield increased accuracy and area under the receiver operating characteristic curve (AUC). The best-known AUC of 0.96 and accuracy of 89.45% were obtained, which are significant improvements over the previous best AUC of 0.87 and accuracy of 76.79%.

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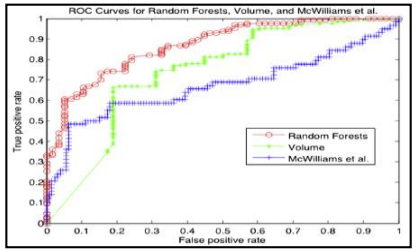
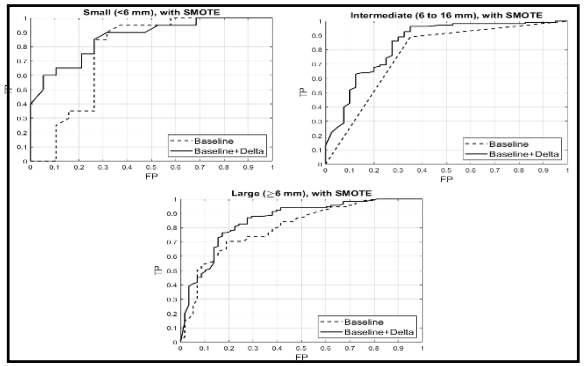
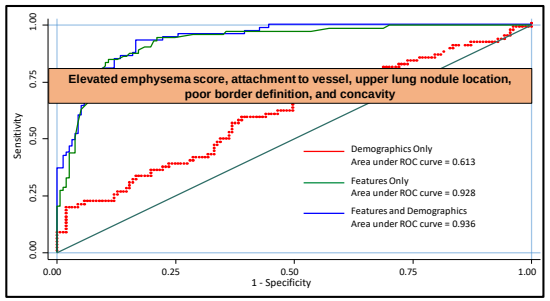
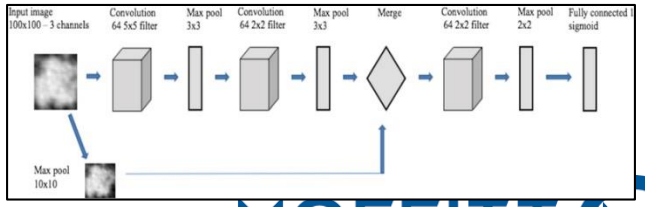
Risk Prediction Publications: Summary

- Using conventional quantitative radiomics, evolving analytics improved AUCs from 0.83 to over 0.90
  - Performed better than volumetric measures and the Brock Model
- Semantic/radiology models yielded AUCs over 0.90
- Delta radiomics (changes over time) improved AUCs vs. using a single timepoint (e.g., from 0.83 to 0.88)
  - Nodule size-specific models also improved AUCs
- Deeply learned models, neural networks, hybrid models, and ensembles yielded AUCs > 0.90 and performed as well as or better than Google's end-to-end results
- Conclusion: Radiomics of standard-of-care images is a robust data source for risk prediction



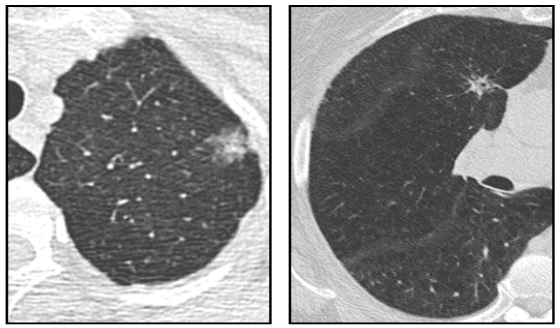






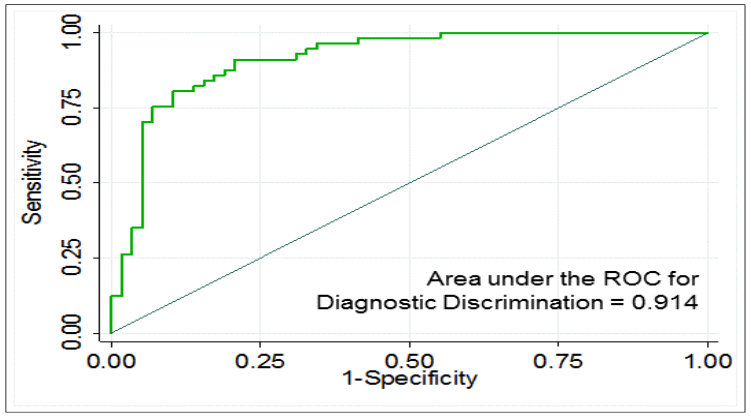
Diagnostic Publications

Quantitative imaging features to discriminate between a benign vs. cancerous nodule

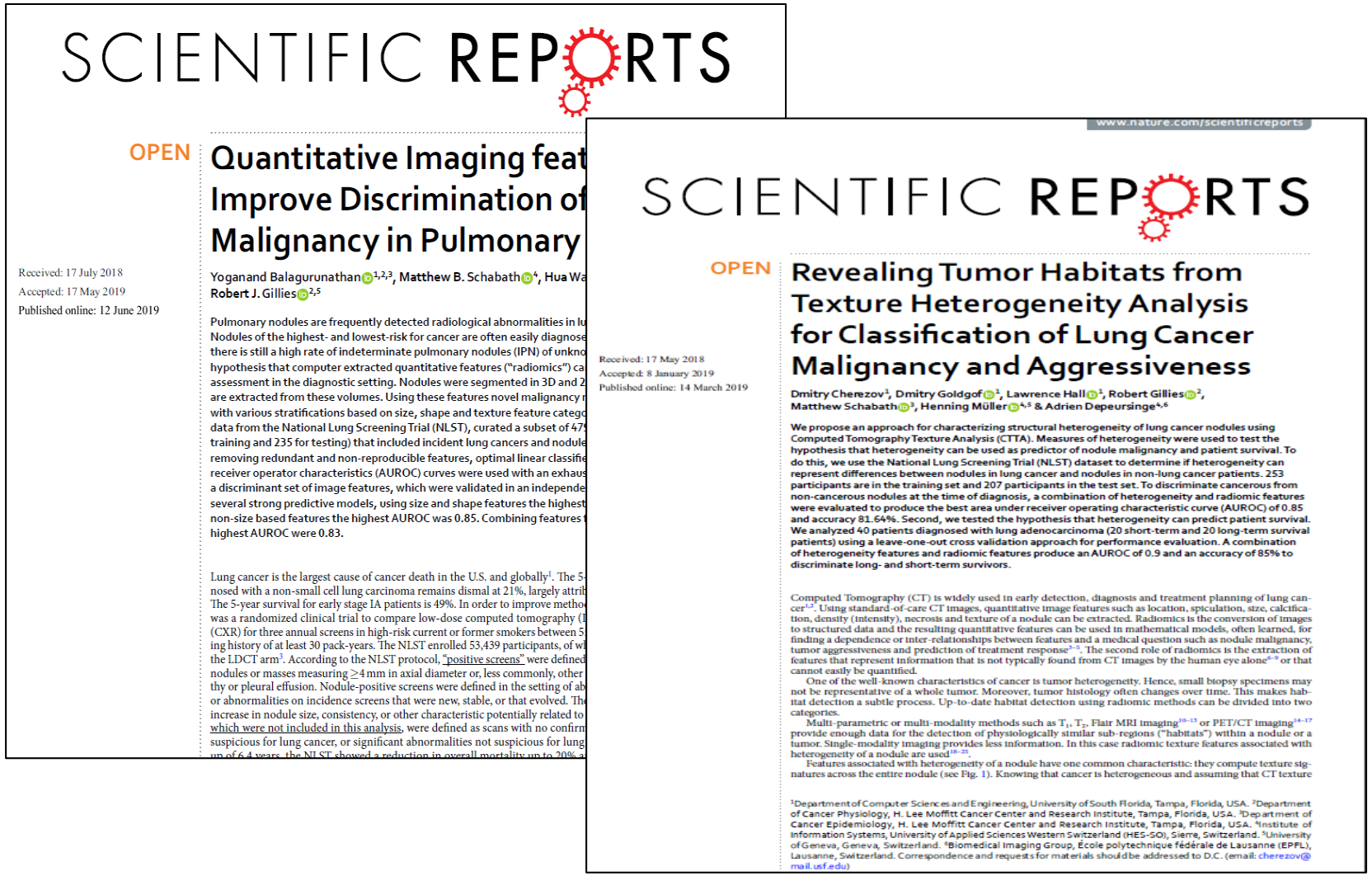


Patient #1: Indeterminate nodule

Patient #2: Lung cancer diagnosis



Diagnostic Publications



SCIENTIFIC REPORTS

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Quantitative Imaging feat
Improve Discrimination of
Malignancy in Pulmonary

Received: 17 July 2018
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Published online: 12 June 2019

Yoganand Balagurunathan[1,2,3], Matthew B. Schabath[4], Hua Wa
Robert J. Gillies[2,5]

Pulmonary nodules are frequently detected radiological abnormalities in lu
Nodules of the highest- and lowest-risk for cancer are often easily diagnose
there is still a high rate of indeterminate pulmonary nodules (IPN) of unkno
hypothesis that computer extracted quantitative features ("radiomics") ca
assessment in the diagnostic setting. Nodules were segmented in 3D and 2
are extracted from these volumes. Using these features novel malignancy r
with various stratifications based on size, shape and texture feature catego
data from the National Lung Screening Trial (NLST), curated a subset of 47
training and 235 for testing) that included incident lung cancers and nodule
removing redundant and non-reproducible features, optimal linear classifie
receiver operator characteristics (AUROC) curves were used with an exhaus
a discriminant set of image features, which were validated in an independe
several strong predictive models, using size and shape features the highest
non-size based features the highest AUROC was 0.85. Combining features
highest AUROC were 0.83.

Lung cancer is the largest cause of cancer death in the U.S. and globally[1]. The 5-
nosed with a non-small cell lung carcinoma remains dismal at 21%, largely attrib
The 5-year survival for early stage IA patients is 49%. In order to improve metho
was a randomized clinical trial to compare low-dose computed tomography (
(CXR) for three annual screens in high-risk current or former smokers between 5
ing history of at least 30 pack-years. The NLST enrolled 53,439 participants, of wh
the LDCT arm[3]. According to the NLST protocol, "positive screens" were defined
nodules or masses measuring ≥4 mm in axial diameter or, less commonly, other
thy or pleural effusion. Nodule-positive screens were defined in the setting of ab
or abnormalities on incidence screens that were new, stable, or that evolved. The
increase in nodule size, consistency, or other characteristic potentially related to
which were not included in this analysis, were defined as scans with no confirm
suspicious for lung cancer, or significant abnormalities not suspicious for lung
up of 6.4 years, the NLST showed a reduction in overall mortality up to 20% a

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Revealing Tumor Habitats from Texture Heterogeneity Analysis for Classification of Lung Cancer Malignancy and Aggressiveness

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Dmitry Cherezov[1], Dmitry Goldgof[1], Lawrence Hall[1], Robert Gillies[2], Matthew Schabath[3], Henning Müller[4,5] & Adrien Depeursinge[4,6]

We propose an approach for characterizing structural heterogeneity of lung cancer nodules using Computed Tomography Texture Analysis (CTTA). Measures of heterogeneity were used to test the hypothesis that heterogeneity can be used as predictor of nodule malignancy and patient survival. To do this, we use the National Lung Screening Trial (NLST) dataset to determine if heterogeneity can represent differences between nodules in lung cancer and nodules in non-lung cancer patients. 253 participants are in the training set and 207 participants in the test set. To discriminate cancerous from non-cancerous nodules at the time of diagnosis, a combination of heterogeneity and radiomic features were evaluated to produce the best area under receiver operating characteristic curve (AUROC) of 0.85 and accuracy 81.64%. Second, we tested the hypothesis that heterogeneity can predict patient survival. We analyzed 40 patients diagnosed with lung adenocarcinoma (20 short-term and 20 long-term survival patients) using a leave-one-out cross validation approach for performance evaluation. A combination of heterogeneity features and radiomic features produce an AUROC of 0.9 and an accuracy of 85% to discriminate long- and short-term survivors.

Computed Tomography (CT) is widely used in early detection, diagnosis and treatment planning of lung cancer[1,2]. Using standard-of-care CT images, quantitative image features such as location, spiculation, size, calcification, density (intensity), necrosis and texture of a nodule can be extracted. Radiomics is the conversion of images to structured data and the resulting quantitative features can be used in mathematical models, often learned, for finding a dependence or inter-relationships between features and a medical question such as nodule malignancy, tumor aggressiveness and prediction of treatment response[3–5]. The second role of radiomics is the extraction of features that represent information that is not typically found from CT images by the human eye alone[6–9] or that cannot easily be quantified.

One of the well-known characteristics of cancer is tumor heterogeneity. Hence, small biopsy specimens may not be representative of a whole tumor. Moreover, tumor histology often changes over time. This makes habitat detection a subtle process. Up-to-date habitat detection using radiomic methods can be divided into two categories.

Multi-parametric or multi-modality methods such as T_1, T_2, Flair MRI imaging[10–13] or PET/CT imaging[14–17] provide enough data for the detection of physiologically similar sub-regions ("habitats") within a nodule or a tumor. Single-modality imaging provides less information. In this case radiomic texture features associated with heterogeneity of a nodule are used[18–25].

Features associated with heterogeneity of a nodule have one common characteristic: they compute texture signatures across the entire nodule (see Fig. 1). Knowing that cancer is heterogeneous and assuming that CT texture

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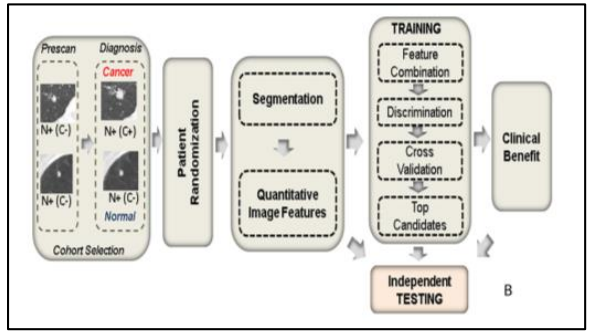
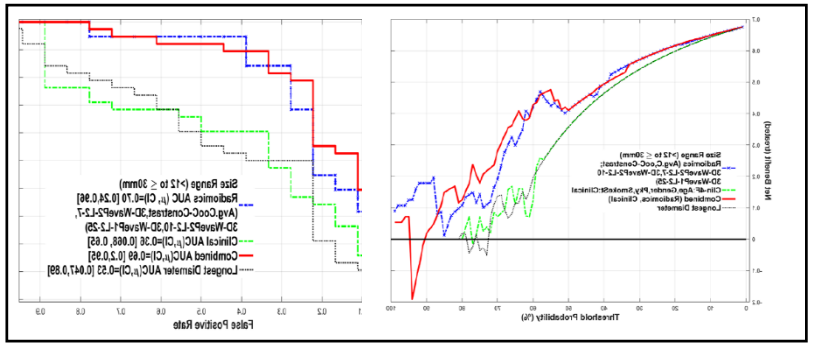
Diagnostic Publications: Summary

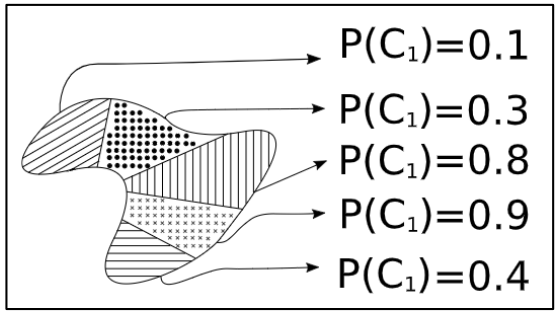
- ML with cross-validation analyses were conducted and strata-specific models on nodule size, shape and texture feature categories:
  - AUCs ranged from 0.80 to 0.85; comparable to same models for risk
  - ML models outperformed LD and volume
  - Risk models = diagnostics in the LCS setting?





- Measures of heterogeneity were developed for diagnostic classification: computed circular harmonic wavelets for small patches to define habitats

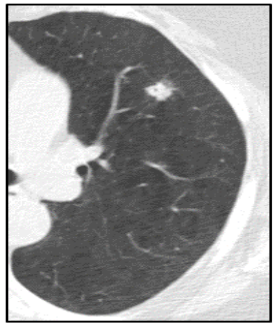
- Combining measures of heterogeneity and conventional radiomics: AUC 0.85



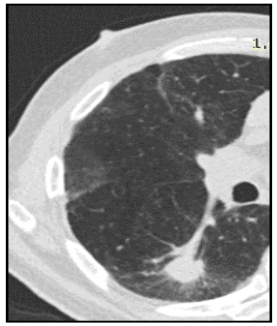
Feature type	Feature set	Feature selector	Classifier	AUROC	Acc. (%)
Staging	NA	NA	NA	0.67	65
Heterogeneity	hV_3	mRMR 1*	J48	0.80	85
Definiens	all 219 features	RfF 5	J48	0.71	77.5
Combined	RIDER $+hV_3$	RfF 5	RFs	0.90	85

Overdiagnosis/Tumor Behavior Publications

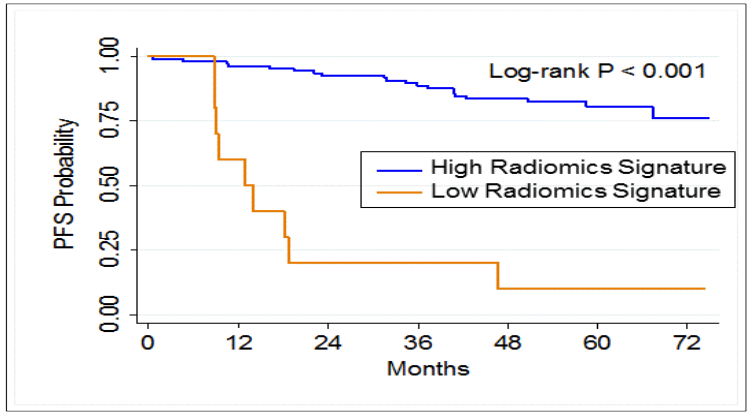
Quantitative imaging features to differentiate aggressive tumors vs. indolent tumors

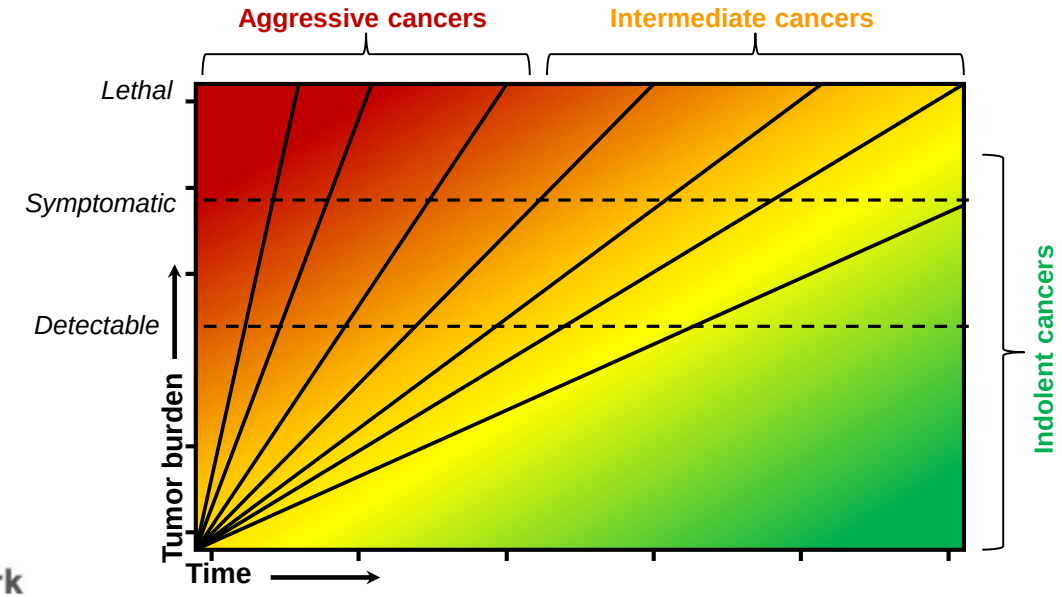


Patient #1
Aggressive early stage lung cancer



Patient #2:
Indolent early stage lung cancer





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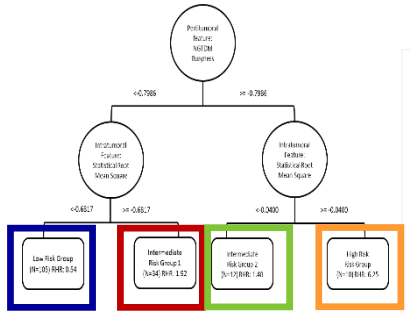
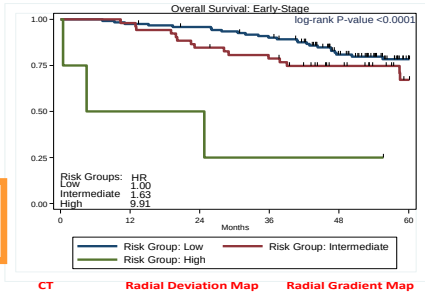
Overdiagnosis/Tumor Behavior Publications

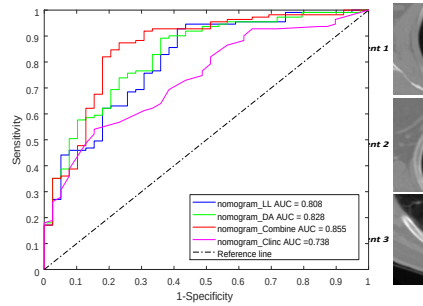
Overdiagnosis/Tumor Behavior Publications: Summary

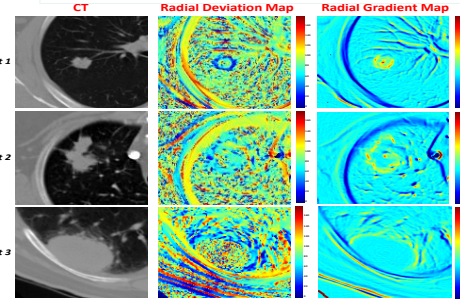
- Decision tree analyses reduced >500 radiomic features into hierarchical classification of 4 risk groups -- High risk subgroup among early stage LC associated with 24% 5-year survival vs. 77% for low-risk (C-index 0.88)

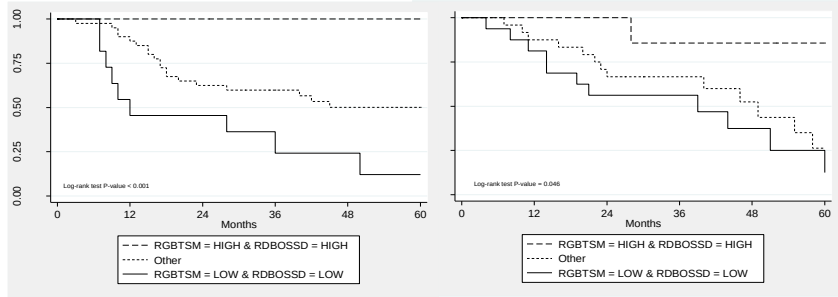




- New approaches:
  1. Calculated radiomics from lung window mask, difference area mask, and combination to differentiate indolent vs. aggressive growing tumors: AUC 0.86
  2. ML identified a novel VDT cut-point to discriminate tumor behavior: aggressive early stage LCs associated with 15-fold increased risk of progression (C-index 0.83)
  3. Developed radial deviation and radial gradient features which capture textural characteristics and semantic differences; validated combinatorial effects of the two most predictive features among non-screen detected adenos
  4. Combining stage, heterogeneity, conventional features discriminated between early vs. late OS: AUC 0.90







Feature type	Feature set	Feature selector	Classifier	AUROC	Acc. (%)
Staging	NA	NA	NA	0.67	65
Heterogeneity	hV_3	mRMR 1*	J48	0.80	85
Definiens	all 219 features	RfF 5	J48	0.71	77.5
Combined	RIDER $+hV_3$	RfF 5	RFs	0.90	85

Advances in Radiomics

Intrinsic dependencies of CT radiomic features on voxel size and number of gray levels

Muhammad Shafiq-ul-Hassan, Geoffrey G. Zhang, and Kujtim Latifi
Department of Physics, University of South Florida, Tampa, FL 33620, USA
H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

Stability and reproducibility of computed tomography radiomic features extracted from peritumoral regions of lung cancer lesions

Ilke Tunali
Department of Cancer Physiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA
Institute of Biomedical Engineering, Bogazici University, Istanbul 34684, Turkey

Lawrence O. Hall

Lung Nodule Sizes Are Encoded When Scaling CT Image for CNN's

Dmitry Cherezov[1], Rahul Paul[1], Nikolai Fetisov[1], Robert J. Gillies[2], Matthew B. Schabath[3], Dmitry B. Goldgof[1], and Lawrence O. Hall[1]

[1]Department of Computer Sciences and Engineering, University of South Florida, Tampa, FL; Departments of [2]Cancer Physiology; and [3]Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Corresponding Author: Dmitry Cherezov, PhD, University of South Florida, 2215 N Spring Glade Cir, Tampa, Florida, USA 33613; Email: cherezov@mail.usf.edu

Key Words: Convolutional neural network, explanation, lung cancer, computed tomography, camera images
Abbreviations: convolutional neural network (CNN), computed tomography (CT),

ABSTRACT

INTRODUCTION

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Author Manuscript

Proc Int Jt Conf Neural Netw. Author manuscript; available in PMC 2018 Nov 13.
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Proc Int Jt Conf Neural Netw. 2018 Jul; 2018: 10.1109/IJCNN.2018.8489440.
Published online 2018 Sep 15. doi: 10.1109/IJCNN.2018.8489440

PMCID: PMC6233304
NIHMSID: NIHMS994309
PMID: 30443437

Representation of Deep Features using Radiologist defined Semantic Features

Rahul Paul,[a] Ying Liu,[d] Qian Li,[d] Lawrence Hall,[a] Dmitry Goldgof,[a] Yoganand Balagurunathan,[c] Matthew Schabath,[b] and Robert Gillies[c]

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Abstract — Go to:

Semantic features are common radiological traits used to characterize a lesion by a trained radiologist. These features have been recently formulated, quantified on a point scale in the context of lung nodules by our group. Certain radiological semantic traits have been shown to extremely predictive of malignancy [26]. Semantic traits observed by a radiologist at examination describe the nodules and the morphology of the lung nodule shape, size, border, attachment to vessel or pleural wall, location and texture etc. Deep features are numeric descriptors often obtained from a convolutional neural network (CNN) which are widely used for classification and recognition. Deep features may contain information about texture and shape, primarily. Lately, with the advancement of deep learning, convolutional neural networks (CNN) are also being used to analyze lung nodules. In this study, we relate deep features to semantic features by looking for similarity in ability to classify. Deep features were obtained using a transfer learning approach from both an ImageNet pre-trained CNN and our trained CNN architecture. We found that some of the semantic features can be represented by one or more deep features. In this process, we can infer that some deep feature(s) have similar discriminatory ability as semantic features.

Keywords: Convolutional neural network, semantic features, deep features

I. Introduction — Go to:

Lung cancer is the leading cause of cancer related deaths globally [1]. For early detection and diagnosis of lung cancers, Low Dose Computed Tomography (LDCT) is the most extensively used imaging approach.

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 56), pp: 96013-96026

Research Paper

Radial gradient and radial deviation radiomic features from pre-surgical CT scans are associated with survival among lung adenocarcinoma patients

Ilke Tunali[1,3,4], Olya Stringfield[1], Albert Guvenis[3], Hua Wang[5], Ying Liu[5], Yoganand Balagurun[1]

[1]Department of
[2]Department of
[3]Institute of Bio
[4]Faculty of Bion
[5]Department o Cancer, Key La
[6]Research Insti

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Keywords: radio
Received: Marc
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ABSTRACT

INTRODUC

Lung can and is the lead United States. I prostate, breast [1]. Despite in

SCIENTIFIC REPORTS

OPEN

Revealing Tumor Habitats from Texture Heterogeneity Analysis for Classification of Lung Cancer Malignancy and Aggressiveness

Dmitry Cherezov[1], Dmitry Goldgof[1], Lawrence Hall[1], Robert Gillies[2],

Received: 17 May 2018
Accepted: 8 January 2019
Published online: 14 March 2019

TOMOGRAPHY

Tomography. 2019 Mar; 5(1): 192–200.
doi: 10.18383/j.tom.2018.00034

PMCID: PMC6403047
PMID: 30854457

Explaining Deep Features Using Radiologist-Defined Semantic Features and Traditional Quantitative Features

Rahul Paul,[1] Matthew Schabath,[2] Yoganand Balagurunathan,[3] Ying Liu,[4] Qian Li,[4] Robert Gillies,[3] Lawrence O. Hall,[1] and Dmitry B. Goldgof[1]

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This article has been cited by other articles in PMC.

Abstract — Go to:

Quantitative features are generated from a tumor phenotype by various data characterization, feature-extraction approaches and have been used successfully as a biomarker. These features give us information about a nodule, for example, nodule size, pixel intensity, histogram-based information, and texture information from wavelets or a convolution kernel. Semantic features, on the other hand, can be generated by an experienced radiologist and consist of the common characteristics of a tumor, for example, location of a tumor, fissure, or pleural wall attachment, presence of fibrosis or emphysema, concave cut on nodule surface. These features have been derived for lung nodules by our group. Semantic features have also shown promise in predicting malignancy. Deep features from images are generally extracted from the last layers before the classification layer of a convolutional neural network (CNN). By training with the use of different types of images, the CNN learns to recognize various patterns and textures. But when we extract deep features, there is no specific naming approach for them, other than denoting them by the feature column number (position of a neuron in a hidden layer). In this study, we tried to relate and explain deep features with respect to traditional quantitative features and semantic features. We discovered that 26 deep features from the Vgg-S neural network and 12 deep features from our trained CNN could be explained by semantic or traditional quantitative features. From this, we concluded that those deep features can have a recognizable definition via semantic or quantitative features.

Keywords: deep features, radiomics, semantic features, interpretation of features, CNN, explainable AI, quantitative features

Introduction — Go to:

Tomography

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Advances in Radiomics

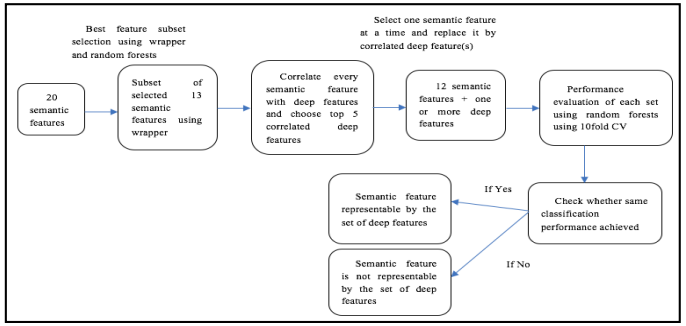
- Already discussed: RD/RG, novel VDTs, heterogeneity habitats, radiomics from different windows, CNN ensembles

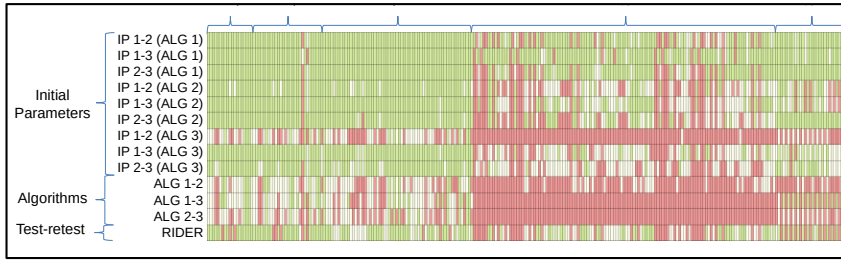
- Defining semantic features by deep learning
  - Performance of the best individual 8 semantic features yielded AUCs 0.82 to 0.84
  - An DL ensemble classified an ensemble of 13 semantic features AUC and accuracy of 0.84

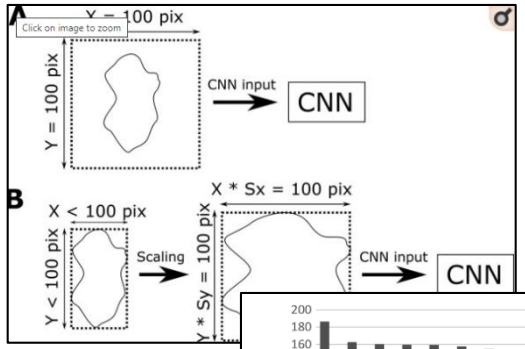
- Methods to identify non-reproducible and unstable radiomics from peritumoral regions of lung lesions
  - Subsets of laws and wavelets appear to be consistently unstable

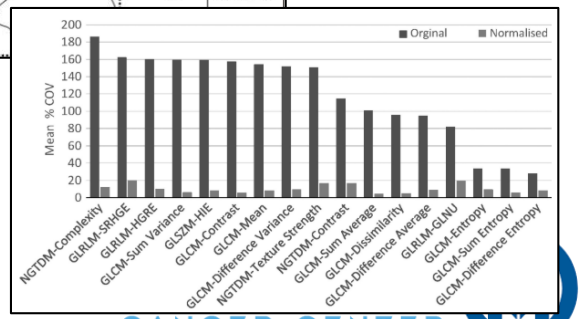
- Lung nodule sizes are encoded when scaling CT image for CNNs: Nodule size is implicitly encodes into texture information, as such size features are likely redundant in models

- Slice thickness and pixel spacing/size may influence reproducibility: Generally, voxel-size resampling is an appropriate pre-processing step; normalizing needed for features that are voxel size and gray-level dependent.



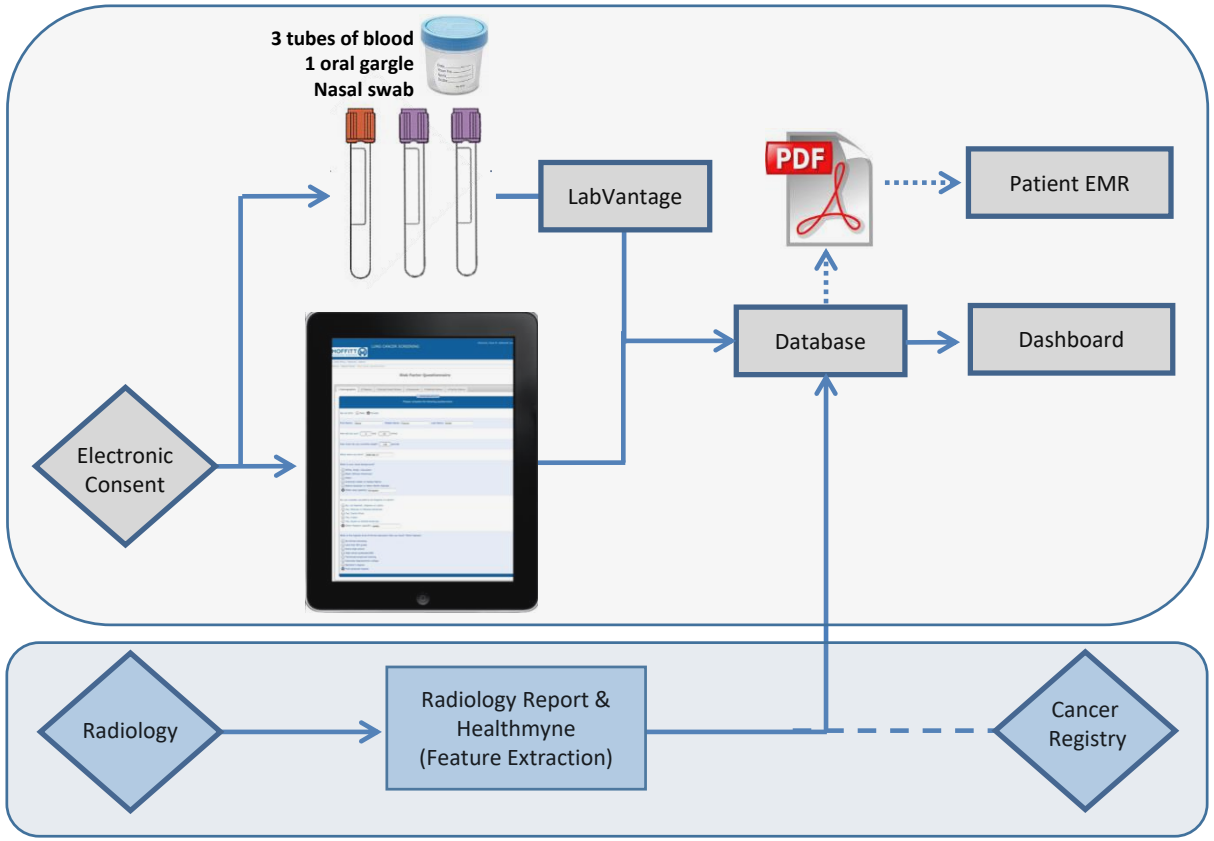






Recruitment Efforts for Aim 2

Prospective Patient Recruitment Workflow



Incidental Pulmonary Nodule Patients

- Total pts: 2,660 retrospective and 200+ prospective
- CT scans curated: 3000+
- Lung cancer Dx: ~40%

Pro/Retro Lung Cancer Screening Patients

- Total pts: 500+
- CT scans curated: 1000+
- Lung cancer Dx: ~4%
- Millennium Health Care: >2100 pts (no blood)

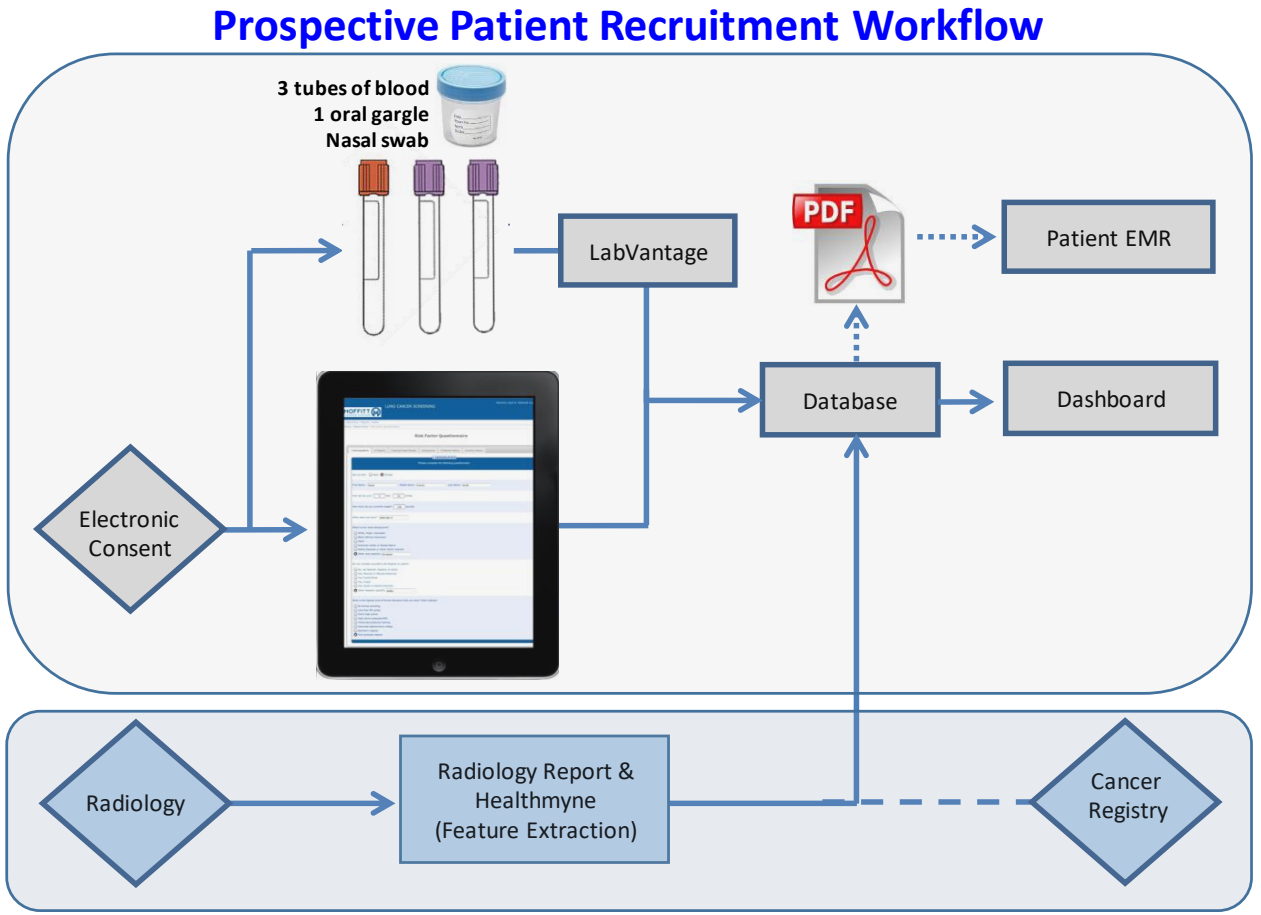
Retrospective cohorts & Prospective recruitment

- Research and clinical data are shared through and integrative workflow
  - Research risk factor survey is stored in the EMR and research database
  - Healthmyne PAC moves CT images, radiology reports, and extracted features in real-time back to the research infrastructure

- Lung cancer screening
  - 460 (403 pros.)
  - Patients that have provided samples: 239
  - Millennium#: 2238 (122 pros.)

- IPN
  - 2780 (196 pros.)
  - Patients that have provided samples: 86

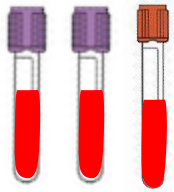
- LTP2
  - 7



Sample Collection

- Oral gargle for methylation markers
- PaxGene (for Wistar)
- Nasal brushing (for BU)

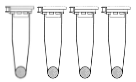
- 2 purple top tubes (10 ml each)
- 1 red top tube are drawn (10 mL each



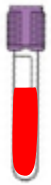
Sample Processing (3 Tubes)

Tube 1: DNA Tube

- *Frozen immediately*
- *DNA isolated in batches of 16*
- *DNA aliquots stored*



DNA aliquots

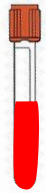


Tube 2: Plasma & Buffy Coat Tube

- *Processed immediately for plasma and buffy*
- *Plasma and buffy coat aliquots stored*

Plasma aliquots

Buffy coat aliquots



Tube 3: Serum Tube

- *Clot for 30 minutes*
- *Processed immediately for serum*
- *Serum aliquots stored*

Serum aliquots

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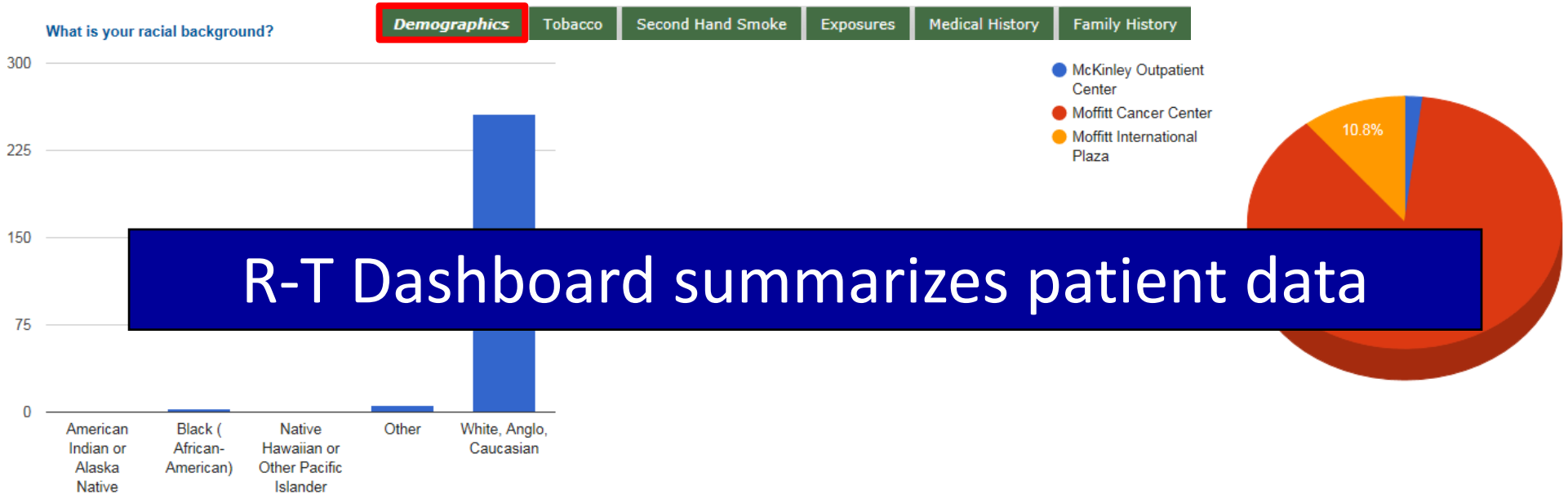
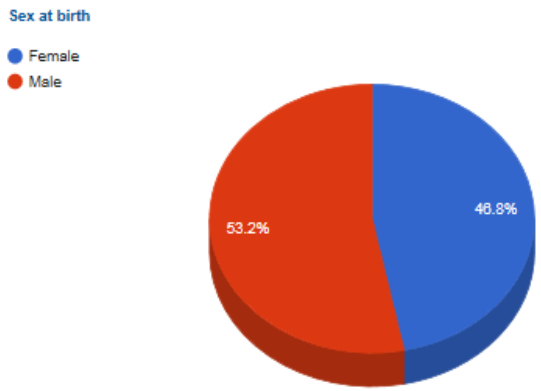
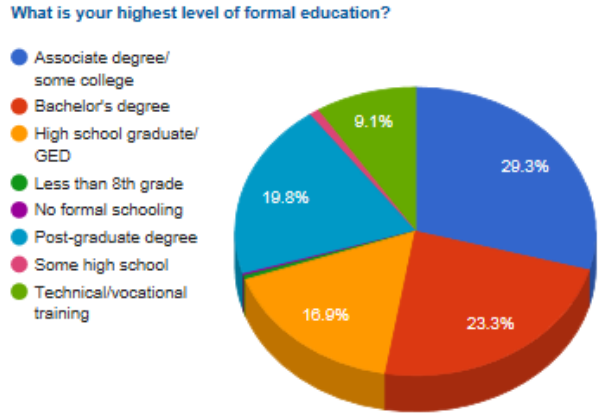
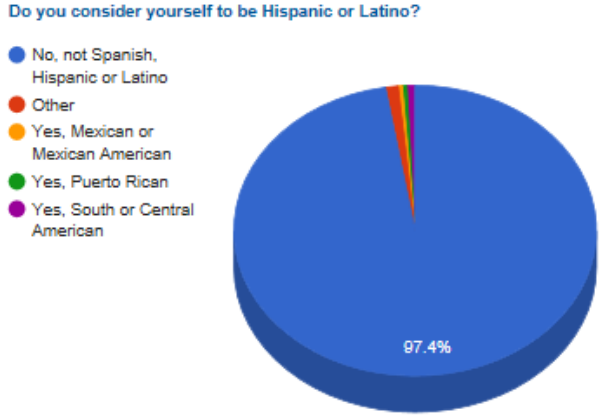
Real-Time Dashboard



R-T Dashboard summarizes patient data







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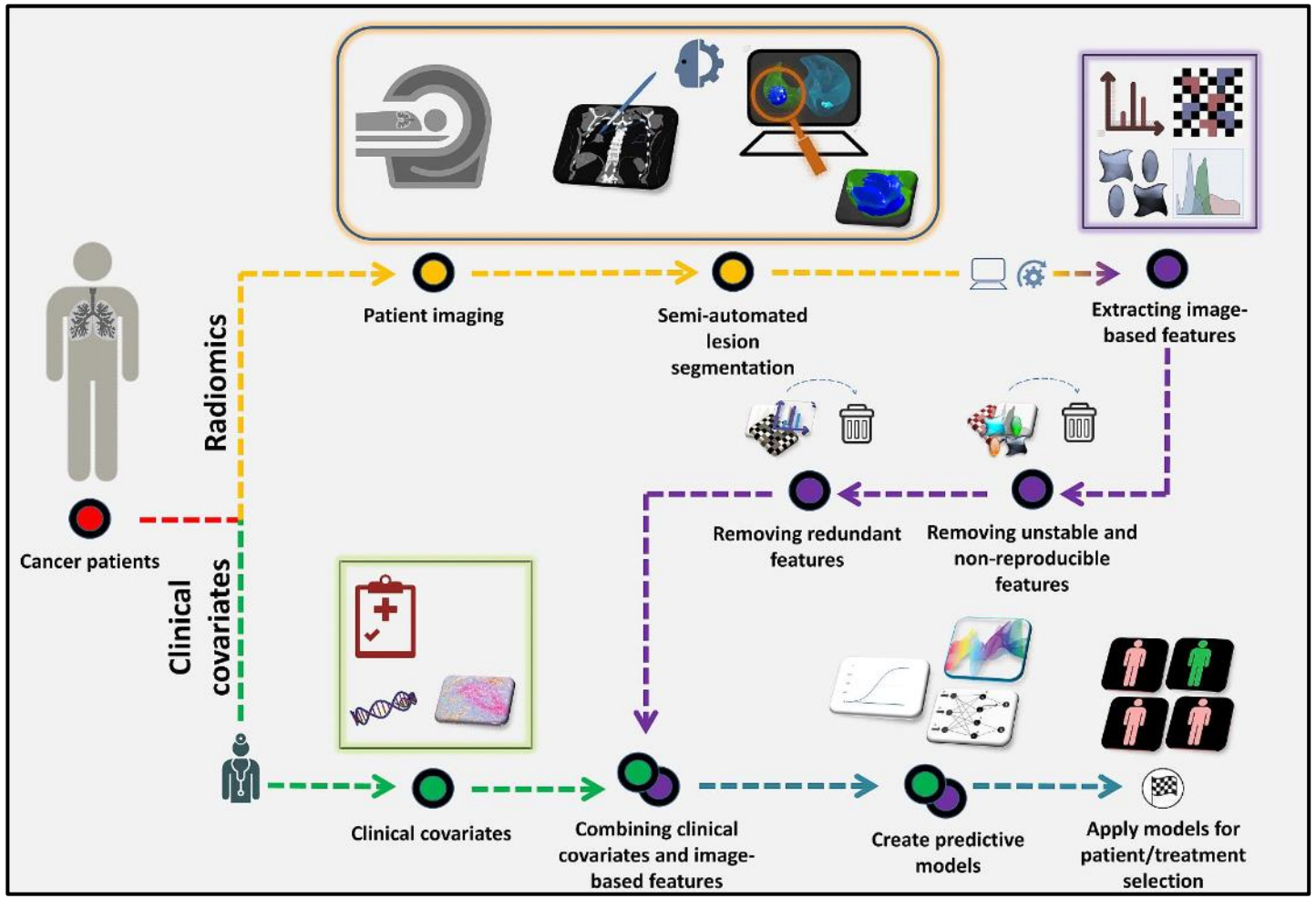
Future Directions

- Transition from conventional radiomics/ROI analyses to deep learning segmentation to whole volumetric image processing*
- Expand parallel efforts into incidental pulmonary nodules*
- Clinical implementation of radiomics*
- Distributed learning*
- Defining biological basis of image features
  - Targeted biopsies for mapping image features to biology
- Integration with circulating and tissue biomarkers and pathomics

Conventional radiomics pipeline



- **Advantages:**
  - Well characterized: stability and reproducibility
  - Successfully classifies at the pixel/voxel level
- **Limitations:**
  - Bottlenecks in Image curation, image segmentation, feature extraction, QA/QC, analysis
- **Solution -> End-to-end DL**
  - CT is the only input
  - Deep learning segmentation and/or whole volumetric image processing
  - DL features and algorithms
- **Sounds easy?**
  - Needs to be benchmarked against current approaches
  - Reproducibility?
  - Stability?
  - Blackbox: Interpretability and biological underpinnings?

ional radiomics pipeline

LETTERS
https://doi.org/10.1038/s41591-019-0447-x
nature medicine
Corrected: Author Correction

End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography

Diego Ardila[1,5], Atilla P. Kiraly[1,5], Sujeeth Bharadwaj[1,5], Bokyung Choi[1,5], Joshua J. Reicher[2], Lily Peng[1], Daniel Tse[1*], Mozziyar Etemadi[3], Wenxing Ye[1], Greg Corrado[1], David P. Naidich[4] and Shravya Shetty[1]

With an estimated 160,000 deaths in 2018, lung cancer is the most common cause of cancer death in the United States[1]. Lung cancer screening using low-dose computed tomography has been shown to reduce mortality by 20–43% and is now included in US screening guidelines[3–6]. Existing challenges include inter-grader variability and high false-positive and false-negative rates[7–10]. We propose a deep learning algorithm that uses a patient's current and prior computed tomography volumes to predict the risk of lung cancer. Our model achieves a state-of-the-art performance (94.4% area under the curve) on 6,716 National Lung Cancer Screening Trial cases, and performs similarly on an independent clinical validation set of 1,139 cases. We conducted two reader studies. When prior computed tomography imaging was not available, our model outperformed all six radiologists with absolute reductions of 11% in false positives and 5% in false negatives. Where prior computed tomography imaging was available, the model performance was on-par with the same radiologists. This creates an opportunity to optimize the screening process via computer assistance and automation. While the vast majority of patients remain unscreened, we show the potential for deep learning models to increase the accuracy, consistency and adoption of lung cancer screening worldwide.

In 2013, the United States Preventive Services Task Force recommended low-dose computed tomography (LDCT) lung cancer screening in high-risk populations based on reported improved mortality in the National Lung Cancer Screening Trial (NLST)[2–5],

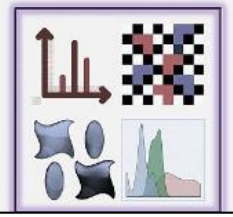
limitations suggest opportunities for mo
to improve performance and inter-read
learning approaches offer the exciting po
complex image analysis, detect subtle holi
unify methodologies for image evaluation

A variety of software devices have
Food and Drug Administration (FDA) v
ing workflow efficiency and performa
detection of lung nodules on lung comp
Clinical research has primarily focused
tion or diagnostic support for lesions ma
ing experts[22–27]. Nodule detection systen
the goal of improving radiologist sensit
ules while minimizing costs to specificity
category of computer-aided detection (
highlights small nodules, leaving malign
clinical decision making to the clinician
pre-identified lesions is included in c
(CADx) platforms, which are primarily a
ficity. CADx has gained greater interest
approvals in other areas of radiology, tho
the time of manuscript preparation[29].

To move beyond the limitations of
approaches, we aimed to build an end-to
ing both localization and lung cancer risk
the input CT data alone. More specifica
replicating a more complete part of a radio

Clinical covariates

Combining clinical covariates and image-based features



- **Advantages:**
  - Well characterized: stability and reproducibility
  - Successfully classifies at the pixel/voxel level

Chair of new Department of Machine Learning

Issam El Naqa, PhD

Chair & Sr. Member
Department of Machine Learning

Demonstrated Leadership and Accomplishments
- Senior Member of the Institute of Electrical and Electronics Engineers (IEEE)
- Fellow of the American Association of Physicists in Medicine (AAPM)
- American Board of Radiology certification in Medical Physics Therapeutics

Education & Training
- Recruited from University of Michigan in 2020 (start date: July 20)
- BS, MS, Electrical Engineering, University of Jordan, Amman, Jordan
- PhD, Electrical Engineering and Computer Science, Illinois Institute of Technology
- MA, Biology, Washington University in St. Louis (Wash U.)
- Postdoctoral Fellow, Radiation Oncology/Medical Physics, Wash U.

Current Extramural Grant Funding
- **R01**, "*Optimal Decision Making in Radiotherapy Using Panomics Analytics*"
- **R37**, "*Combined radiation acoustics and ultrasound imaging for real-time guidance in radiotherapy*"

170+ Publications
- Including recent work in *Medical Physics, JCO Clinical Cancer Informatics, Int J of Radiat Onc Biol Phys*

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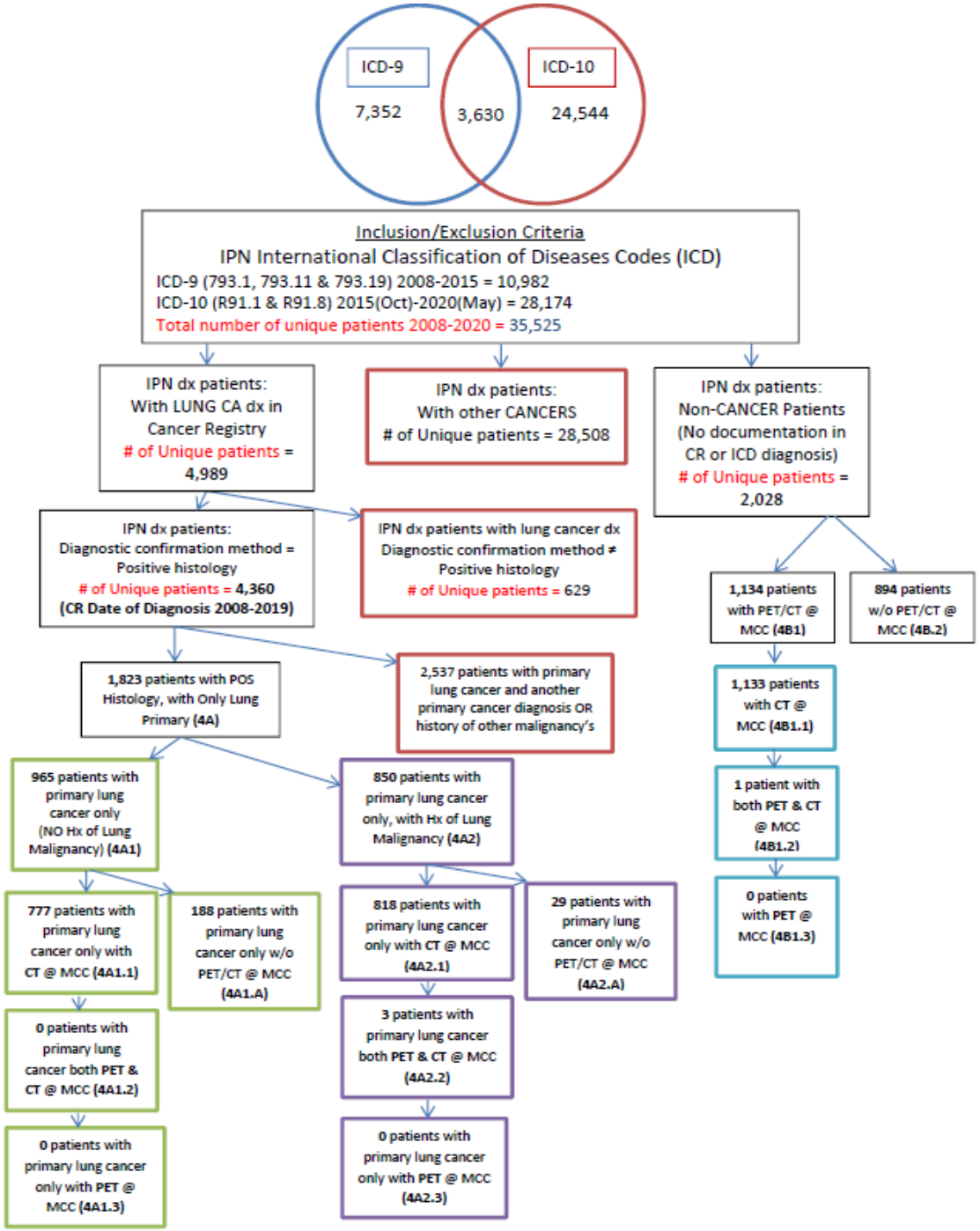

Incidental Pulmonary Nodules

- Encountered commonly in routine cross-sectional imaging: 1.5 million adults/year
- Challenges to manage IPNs parallel lung cancer screening:
  - probability of cancer
  - aggressive behavior of the cancer
- Answer to these challenges often justifies diametrically opposed strategies:
  - biopsy vs. follow-up
  - resection +/- adjuvant treatment
- Each carries consequences including:
  - early detection, cure of the cancer, and morbidities from invasive procedure
  - overtreatment

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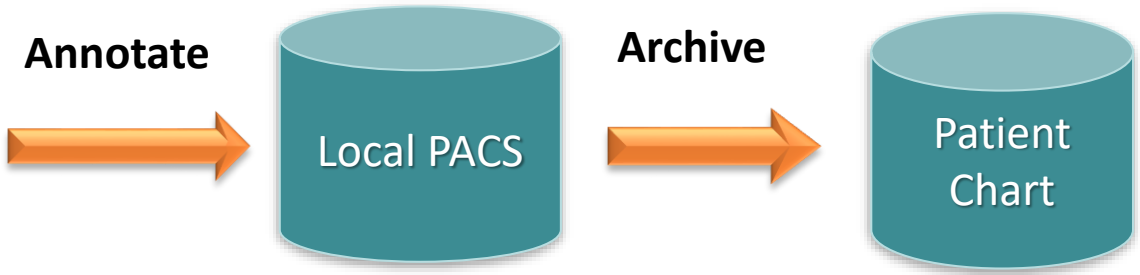
Clinical implementation of radiomics



Clinical implementation of radiomics

Annotate

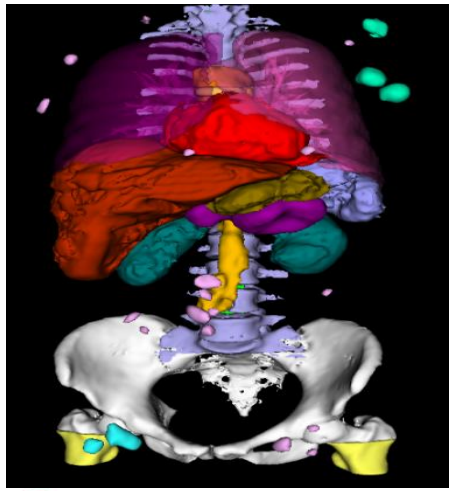
Local PACS

Archive

Patient Chart

Clinical Decision Support

Accept or modify segmentation



Extract features

Genomic Data

Medical Data

Radiomic Data

Databasing + Decision Support Algorithms

How do we get here?

- Radiomics works
- Retrospective case-control evidence is overwhelming
- Next step: Clinical utility tested by multisite observational trial across

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Distributed learning (is the future)

- Multi-institutional validation of radiomics models is slowed down due to privacy concerns of sharing medical images and transferring and managing LARGE databases (>= terrabytes)
- Share algorithms not data
- Conceptually, not new: Statisticians/Pop Scientists have shared models for decades
- Decentralized approach can achieve the identical results as a fully centralized approach.


Radiotherapy and Oncology 121 (2016) 459–467

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Distributed learning

Distributed learning: Developing a predictive model based on data from multiple hospitals without data leaving the hospital – A real life proof of concept

Arthur Jochems [a,*,1], Timo M. Deist [a,b,1], Johan van Soest [a,b], Michael Eble [c], Paul Bulens [d], Philippe Co
Wim Dries [f], Philippe Lambin [a,b,1], Andre Dekker [a,1]

[a] Department of Radiation Oncology (MAASTRO Clinic), Maastricht; [b] GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The N
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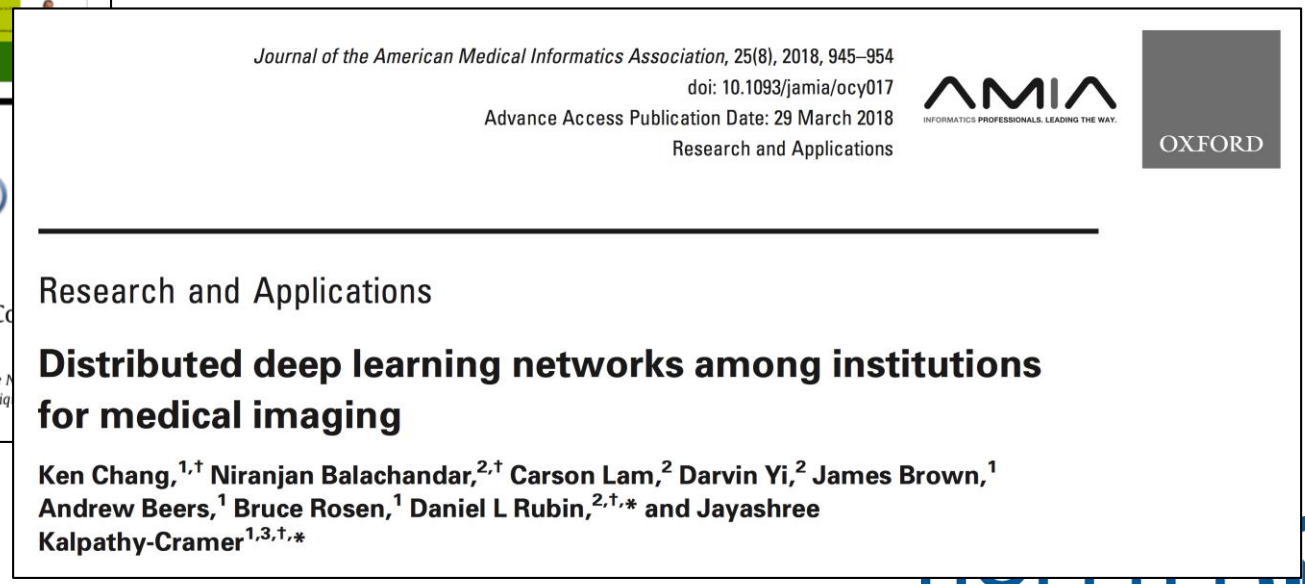
(CHU de Liège), Belgium; and [f] Catharina-Hospital Eindhoven, The Netherlands


Journal of the American Medical Informatics Association, 25(8), 2018, 945–954
doi: 10.1093/jamia/ocy017
Advance Access Publication Date: 29 March 2018
Research and Applications

AMIA INFORMATICS PROFESSIONALS. LEADING THE WAY.

OXFORD

Research and Applications

Distributed deep learning networks among institutions for medical imaging

Ken Chang,[1,†] Niranjan Balachandar,[2,†] Carson Lam,[2] Darvin Yi,[2] James Brown,[1] Andrew Beers,[1] Bruce Rosen,[1] Daniel L Rubin,[2,†,*] and Jayashree Kalpathy-Cramer[1,3,†,*]

Conclusions and Challenges

- Conclusion 1: Radiomics of standard of care images can greatly improve risk, diagnosis, and prognosis (reduce overdiagnosis)
- Conclusion 2: Radiomics is very much a dynamic and evolving discipline with extensions to deep learning/AI

- Challenge 1: Addition of circulating, tissue, and pathology biomarkers for improved performance
- Challenge 2: Parsimony in number of features in a model
- Challenge 3: Numbers are King, Quality is Queen
- Challenge 4: Prospective observational and intervention trials to determine clinical utility and decision support systems
- Challenge 5: Distributed learning

Lung Cancer Radiomics Team

Moffitt

- Bob Gillies, PhD, (MPI)
- Yoga Balagurunathan, PhD, (Co-I)
- Ilke Tunali, PhD, Postdoc
- Jaileene Perez-Morales, PhD, Postdoc
- Olya Stringfield, PhD, Imaging Scientist
- Mahmoud Abdallah, Imaging Scientist
- Alberto Garcia, Data Manager

Tianjin

- Zhaoxiang Ye, MD, Radiologist
- Ying Liu, MD, Radiologist
- Hua Wang, MD, Radiologist
- Jin Qi, MD, Radiologist
- Qian Li, MD, Radiologist
- Hung Lu, MD, Radiologist

USF

- Dmitry Goldgof, PhD, Computer Scientist
- Larry Hall, PhD, Computer Scientist
- Dmitry Cherezov, PhD Candidate
- Sam Hawkins, PhD, Computer Scientist
- Rahul Paul, PhD, Computer Scientist

Vanderbilt

- Pierre Massion, MD, Pulmonologist

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- Deni Aberle, MD, Radiologist

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