Lung collaborative group report

Early Detection Research Network

July 1, 2020

35th steering committee meeting

Lung Collaborative Group

Early Detection Research Network

Biomarker Development Laboratories	
Steve Dubinett, Marc Lenburg, Deni Aberle, Avi Spira	BU, UCLA and Lahey Clinic
Louise Showe, Qihong Huang	Wistar Institute
Jim Herman, Tom Pisanic, Brenda Hoegaarde, Jeff Wang	U of Pittsburgh, Hopkins
Harvey Pass, Haining Yang	NYU
Biomarker Reference Laboratory	
Sanford Stass, Feng Jiang	University of Maryland
Clinical Validation Centers	
Pierre Massion, Eric Grogan, Steve Deppen, Melinda Aldrich	Vanderbilt
Bob Gillies, Matt Schabath, John Heine, Jay Lee	Moffitt CC
DMCC	
Tracey Marsh, Jackie Dahlgren, Margaret Pepe	Fred Hutchinson CC
Program Officers	
Lynn Sorbara	NCI DCP
Karl Krueger	NCI DCP

UPMC BDL

Jim Herman
Tom Pisanic- JHU
Jeff Wang
David Wilson
Brenda Hoegaarde

Jim Herman, MD

Tom Pisanic PhD

Jeff Wang, PhD

Brenda Diergaarde, PhD

Circulating methylated DNA-based biomarkers for early detection of lung cancer

Best **analytical Sensitivity**

Plasma DNA Methylation Detection on screening detected Small nodules

A new level of sensitivity (163 cancer, 83 benign)

Stage I NSCLC nodule size (all ≤ 3.0 cm)

Plasma	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
CDO1	63%	83%	88%	53%	0.78	(0.71 - 0.83)
TAC1	68%	70%	81%	57%	0.71	(0.64 - 0.78)
SOX17	68%	86%	90%	57%	0.82	(0.76 - 0.87)
HOXA7	55%	87%	89%	50%	0.73	(0.67 - 0.80)
CD01, TAC1, SOX17	**89%**	**61%**	**82%**	**74%**	**0.85**	**(0.81 - 0.91)**
CD01, HOXA7, SOX17	**90%**	**71%**	**86%**	**78%**	**0.88**	**(0.84 - 0.93)**

CD01, HOXA7, SOX17	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
T 2.1-3.0 cm	91%	90%	96%	81%	0.95	(0.57 - 0.84)
T 1.1-2.0 cm	74%	93%	90%	63%	0.92	(0.74 - 0.94)
T 0 - 1.0 cm	64%	82%	82%	64%	0.75	(0.62 - 0.89)

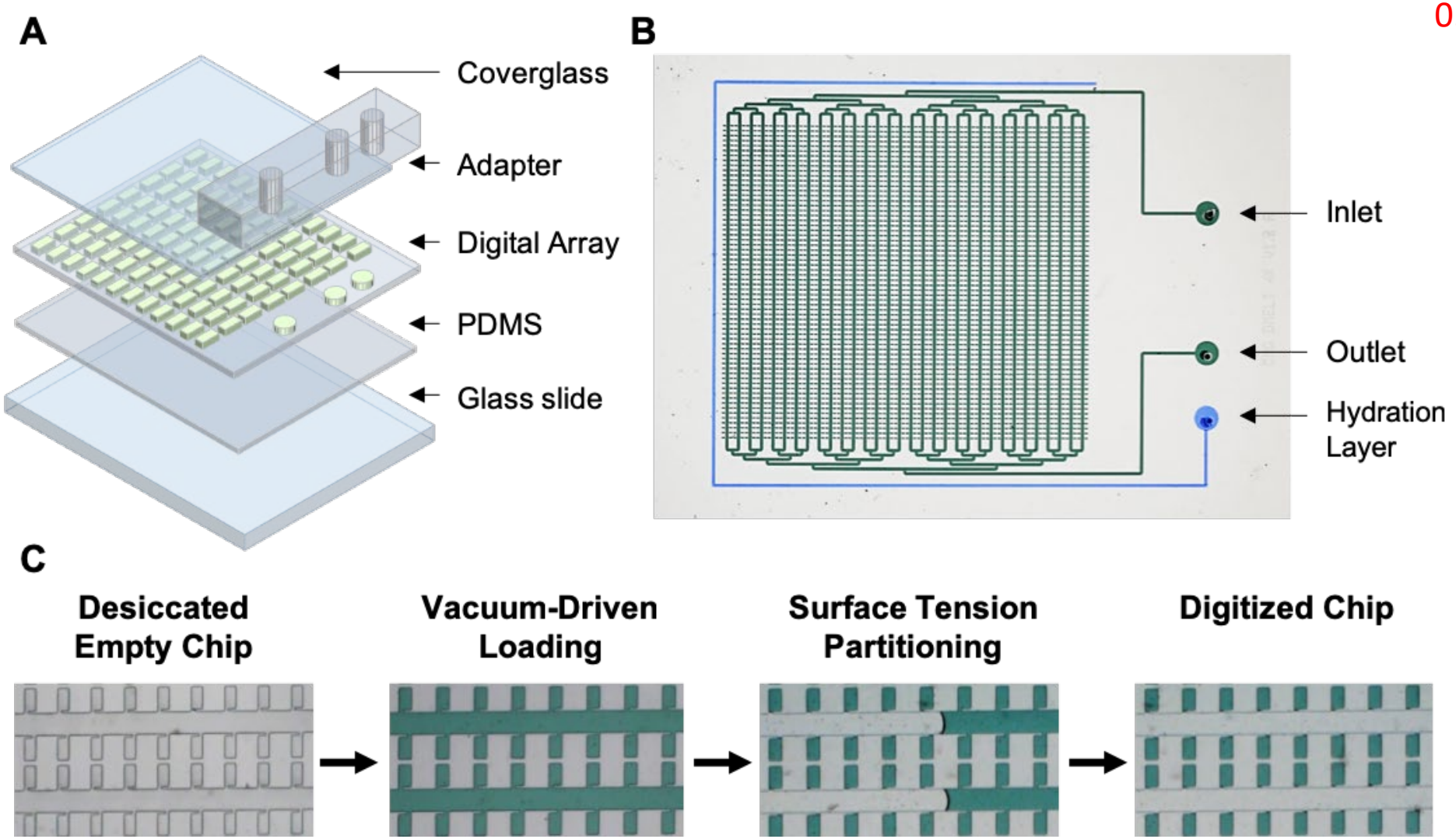
CDO1, SOX17, TAC1						
T 0 - 1.0 cm	**71%**	**82%**	**83%**	**69%**	**0.81**	**(0.69 - 0.93)**

Chen et al, Clinical Epigenetics, 2020

Microfluidic Digitization

Increasing Sensitivity further using 4096-well array

Combined with DREAMing
0.0005%



O'Keefe, et.al. *Sci. Advances* (2018)

BU-UCLA
BDL

Avi Spira
Steve Dubinett
Marc Lenburg
Deni Aberle


Avi Spira MD


Steve Dubinett, MD


Marc Lenburg, PhD


Deni Aberle, MD

Epithelial-based markers of lung cancer early detection

Best **integration with other Networks**

miRNAs for the diagnosis of lung cancer among IPNs

miRs	log2_FC	FDR	PV			Literature
			UCLA miR-seq		BU miR-seq	
			Tumor ≤ 2cm	Tumor > 2cm		
hsa-let-7f-5p	-0.40	0.024	0.71	0.57	0.25	down in NSCLC (PMID: 20595154)
hsa-miR-1207-5p	0.50	0.045	N/A	N/A	N/A	
hsa-miR-141-3p	0.47	0.024	0.41	**0.03**	**0.01**	Poor prognosis in early state ADC (PMID: 25003366)
hsa-miR-151a-5p	-0.25	0.045	0.30	0.64	0.10	
hsa-miR-200a-3p	0.59	0.024	0.27	**0.07**	**0.01**	Regulating EMT,
hsa-miR-205-5p	0.71	0.028	0.01	0.004	0.61	Regulating EMT, ADC specific miRNA (PMID: 25695220)
hsa-miR-339-3p	-0.44	0.035	0.78	0.24	0.87	
hsa-miR-34a-3p	0.43	0.024	N/A	N/A	N/A	
hsa-miR-374a-5p	-0.24	0.029	0.39	0.01	0.19	Targeting PTEN in late stage NSCLC (PMID:29362431)
hsa-miR-375	0.66	0.028	0.60	**0.05**	**0.03**	SCC specific miRNA (PMID: 25695220)
hsa-miR-450a-5p	0.48	0.028	0.40	0.03	0.64	
hsa-miR-596	0.29	0.035	N/A	N/A	N/A	
hsa-miR-616-5p	0.31	0.024	0.45	0.11	N/A	

180 nodules

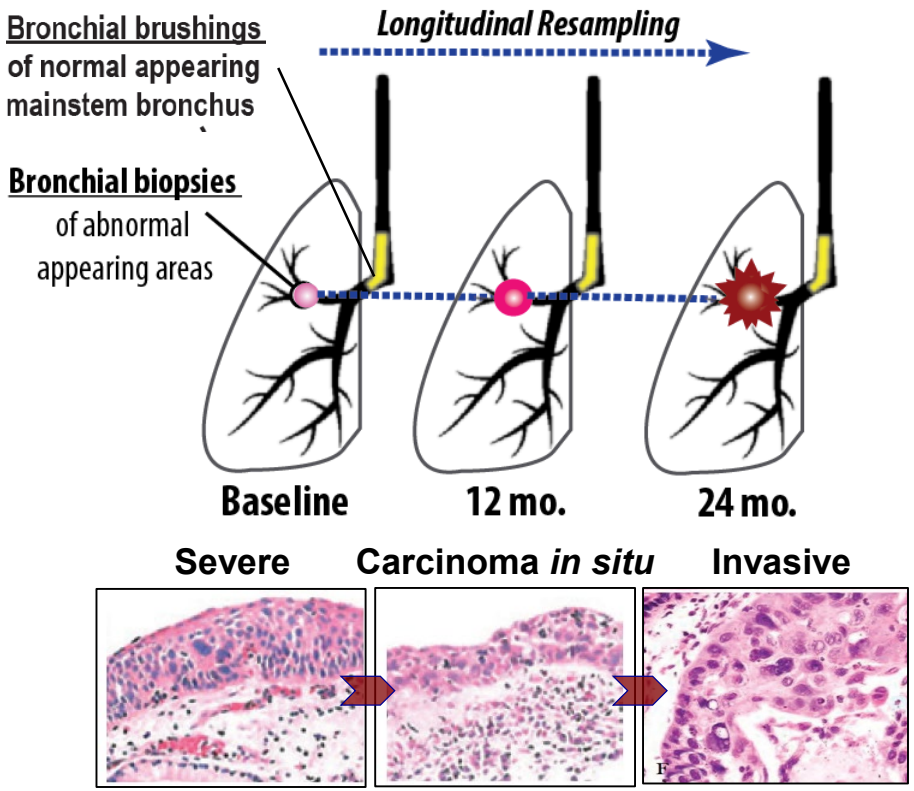
Selected as top 10 genes

>90/100

70-90/100

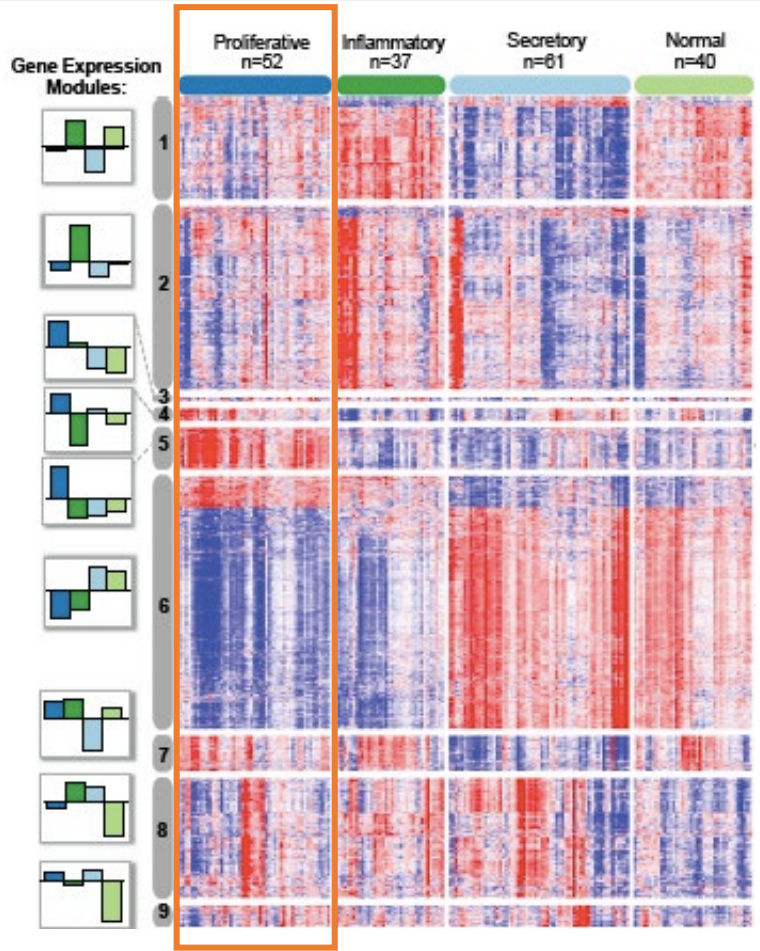
Linking the “field” to the premalignant lesion via the Lung Pre-Cancer Atlas (SU2C Dream Team; NCI PCA; JNJ)

Study Design

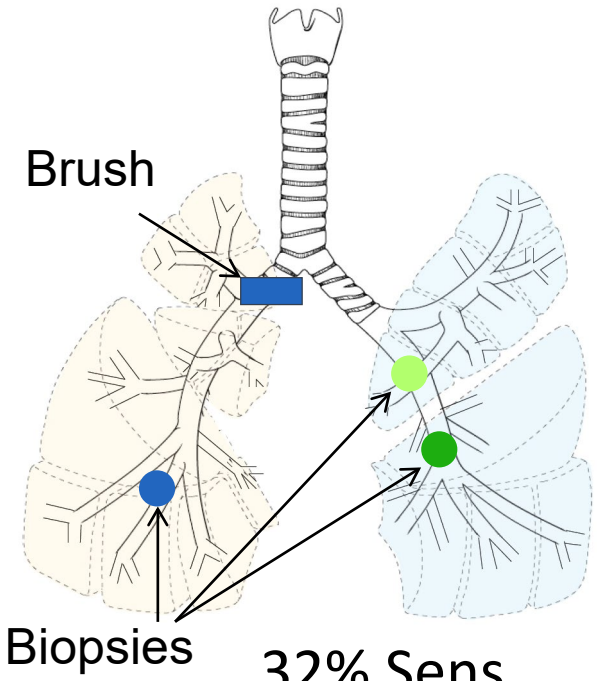


Beane et al. Nature Communications. 2019.

Biopsy-derived Molecular Subtypes



Bronchial Brushes Reflect Lesion Proliferative Subtype

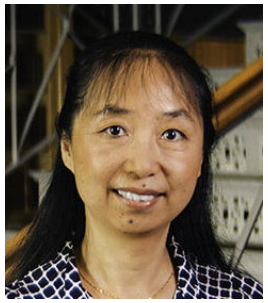


32% Sens.
91% Spec.

Wistar BDL

Louise Showe
Qihong Huang
Qin Liu

Louise Showe, PhD

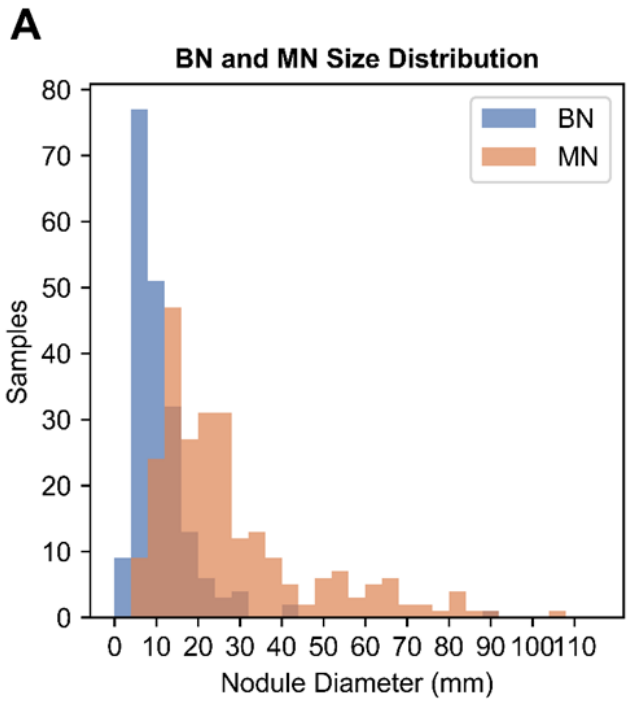


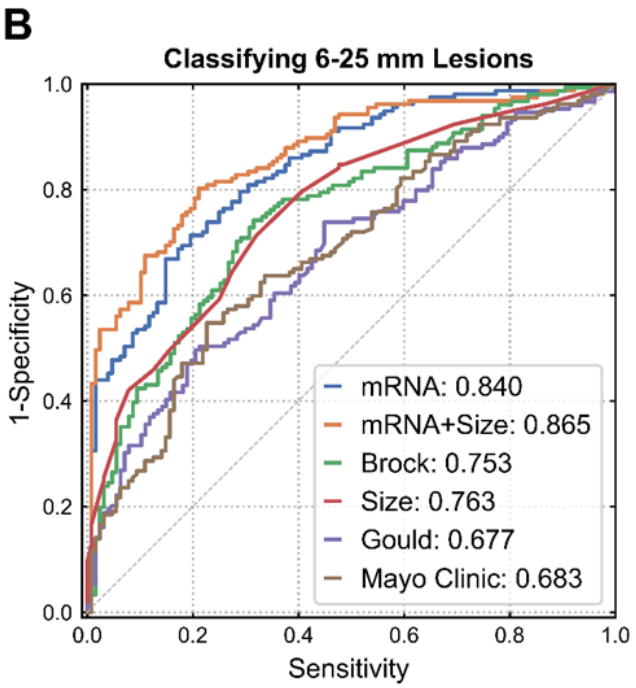
Qin Liu, MD, PhD

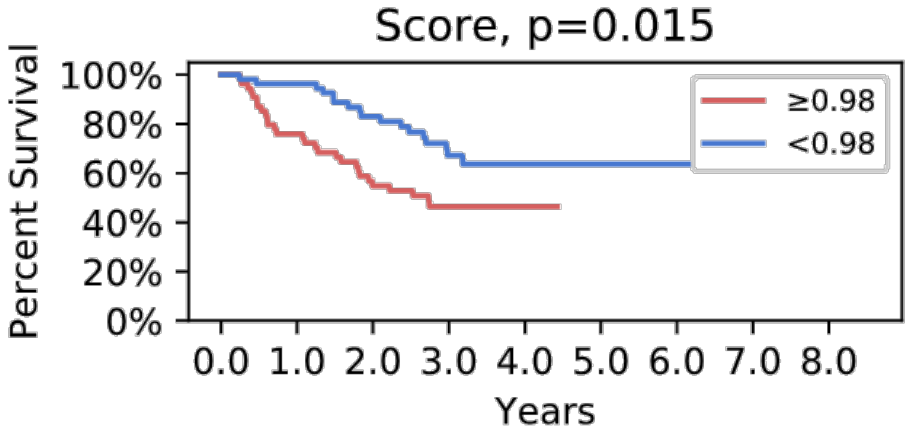
PBMC mRNA-based markers for early detection of lung cancer

Best use of **PAXGENE tubses**

mRNA Lung Nodule classifier from whole blood training set n=400 , Testing set n=133







New NanoString Classifier

- 420 Probes (380 diagnostic, 20 Housekeeping, 20 prognostic)
  - Probe IDs to be standardized in all batches of reagents as for a clinical test
  - Artificial internal standard (Single-Patient Reference-Based Strategy for Batch Effect Correction: PLoS ONE 2015) duplicates run on each cartridge
- 410 samples for Stage 1 development (selecting best probes)
  - 50% MN and 50% BN
  - 250 samples for Training (Done) 160 samples for Testing (in progress)
  - Select the most informative probes
- Stage 2: Finalize a classifier with smallest number of probes returning highest accuracy
  - Order new custom panel
  - Test 1400 samples including LTP2 samples

Harvey Pass, MD

Haining Yang, MD, PhD

NYU BDL

Harvey Pass
Haining Yang

Best **ROC curves**

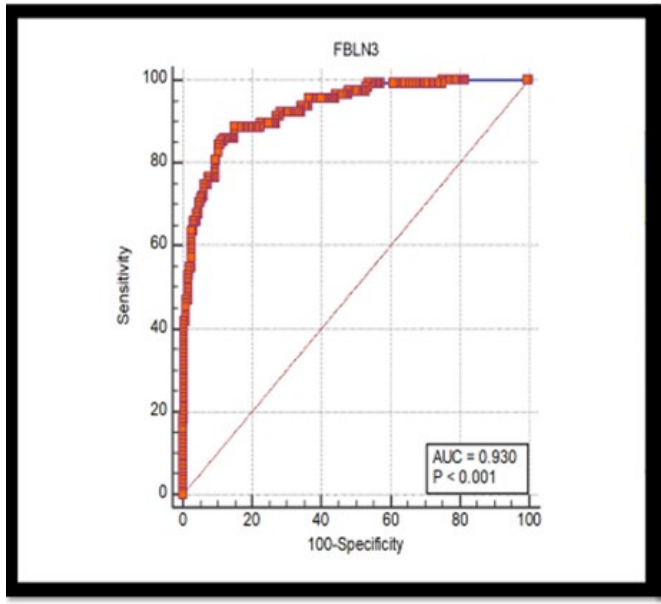
Blood-based biomarkers for early detection of mesothelioma and lung cancer

NYU-Hawaii BDL: Fibulin 3 plasma levels for Diagnosis of MPM

- **Mesothelioma**
- New ELISA developed at NYU with Fibulin mAB mAB428.2

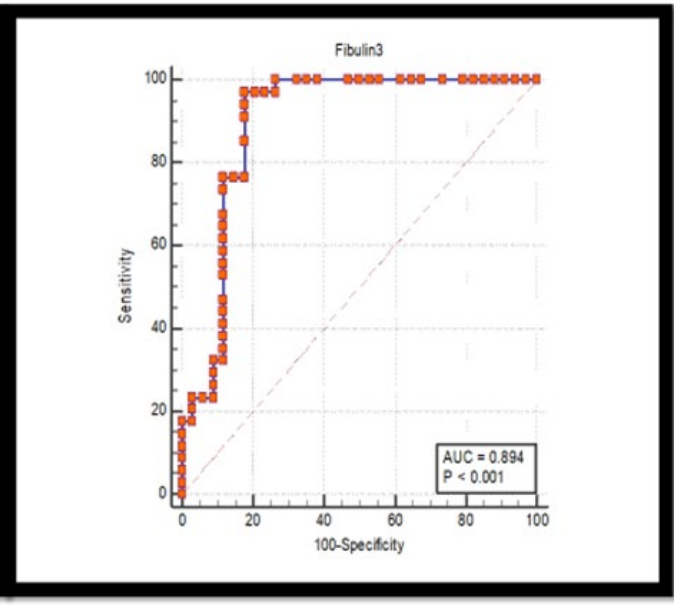
		Meso Pre (ven)	Meso Intraop (Art)	All Meso (ven&art)
	N	47	89	115
Sinai Asbestos Exposed (ven)	110	0.986	0.915	
Yale Non Meso PE plasma (ven)	36	0.950		
NYU Non Meso PE Plasma (Art)	48		0.899	0.917
NYU Non Meso PE Benign Plasma (Art)	15		0.865	
Non Meso PE Cancer Plasma (Art)	33		0.896	
All Non Meso (ven & art)	194			0.929

All NYU Meso Plasma (115) Vs All Non Meso Plasma (192)



307

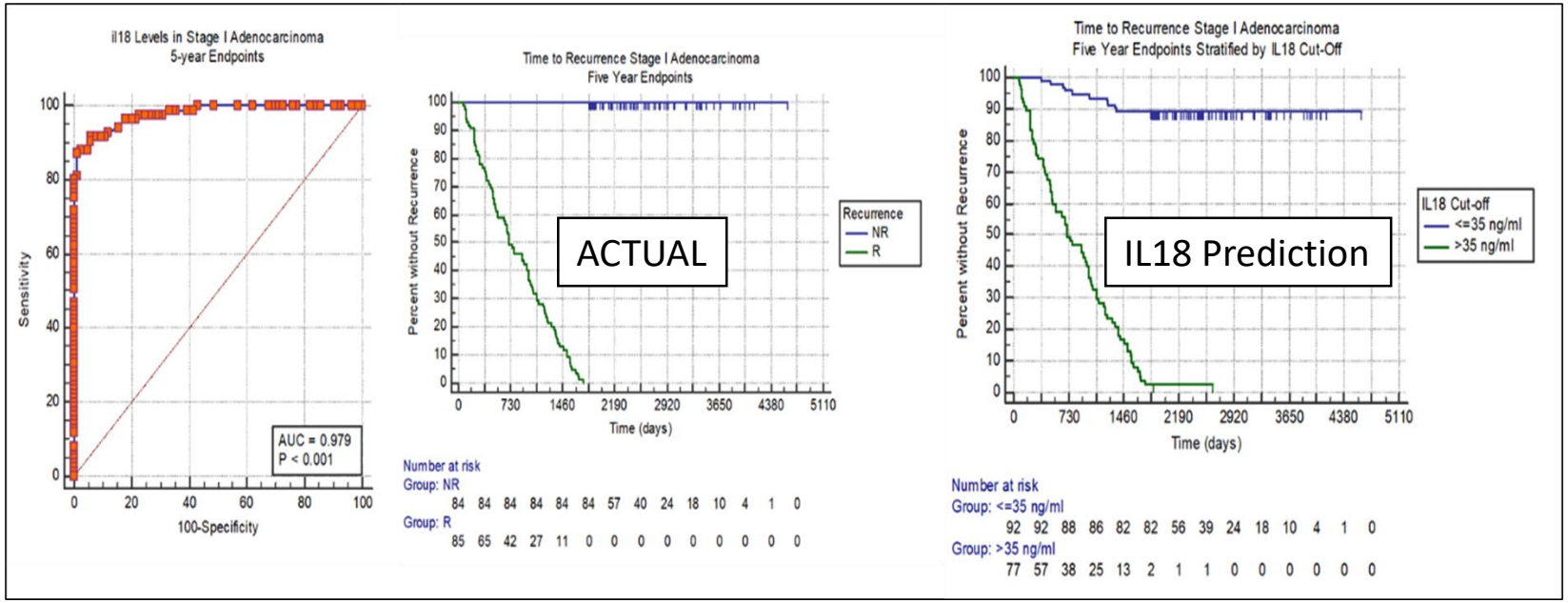
Blinded Validation University Pennsylvania
MM (61) vs Non Meso High Risk (34)



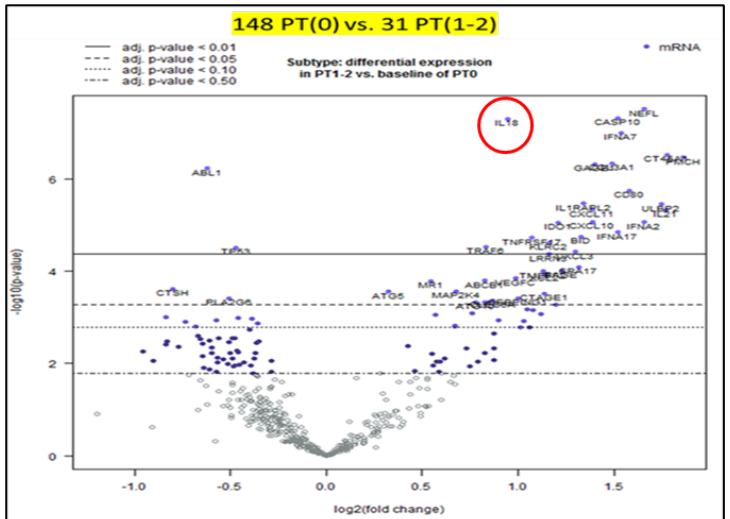
95

NYU-Hawaii BDL: IL-18 predicts Recurrence in pStage I ADC

Plasma IL-18 at Surgery forecasts recurrence if level is >35 ng/ml (all patients with at least 5-year follow-up



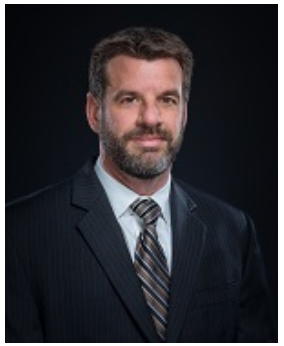
Discovery: Buffy Coat Immunotranscriptomics
No Recurrence vs Recurrence



- <u>Blinded Validation Sought:</u>
  - Pierre Massion, in progress
  - Any other EDRN sites?
  - NLST???
- <u>Future Questions</u>
  - Where is the IL-18 coming from?
    - IHC
    - Digital Spatial Profiling
    - In Vitro Co-Culture Experiments

Moffitt CVC

Schabath
Gillies
Heine
Lee


Matt Schabath, PhD


Bob Gillies, PhD


John Heine, PhD


Jae Lee, PhD

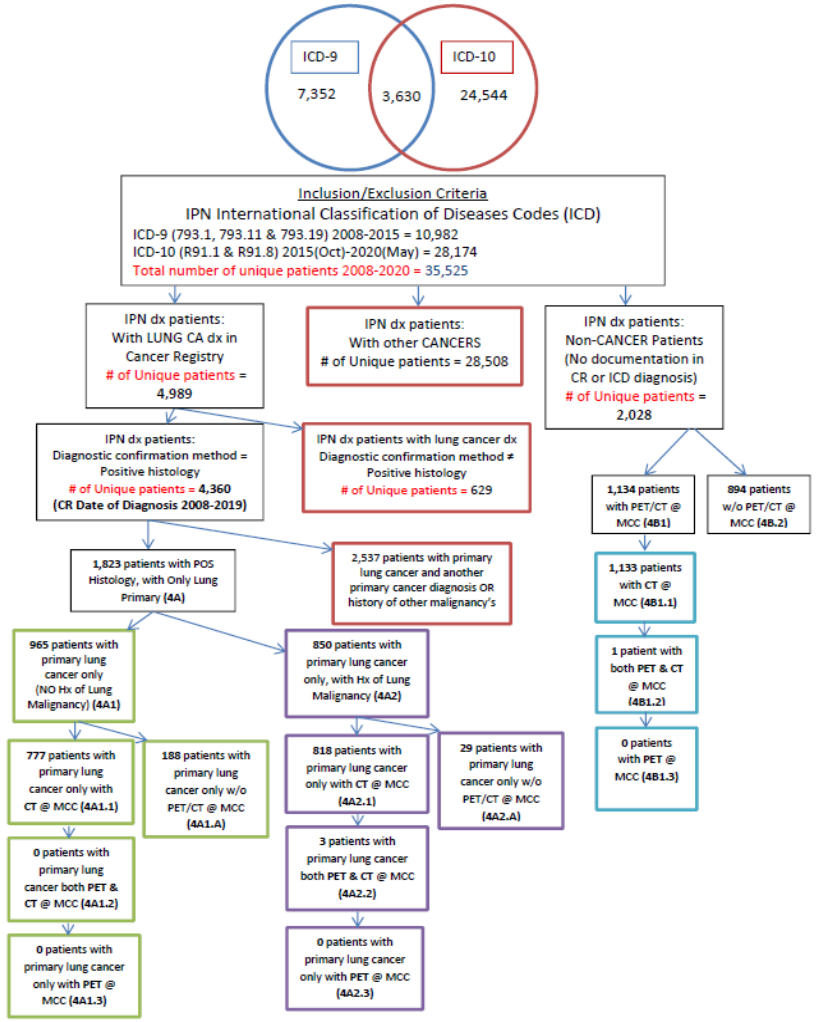
Developing an End-to-End Deep Learning Pipeline for Incidentally-Detected Pulmonary Nodules

Best **Intelligence, somehow artificial**

Incidentally-Detected Pulmonary Nodules (IPNs)

- IPNs encountered commonly in routine cross-sectional imaging: ~1.5 million adults/year
- Challenges to manage IPNs parallel challenges in lung cancer screening:
  - probability of cancer
  - aggressive behavior of the cancer
- Radiomics have unequivocally been successful in addressing these challenges in lung cancer screening
- AI methods will be needed to tackle this problem because IPN patients are innumerable: **31K over 11 years from a single institution!**

Schema of IPNs over 11 years (N>31K)



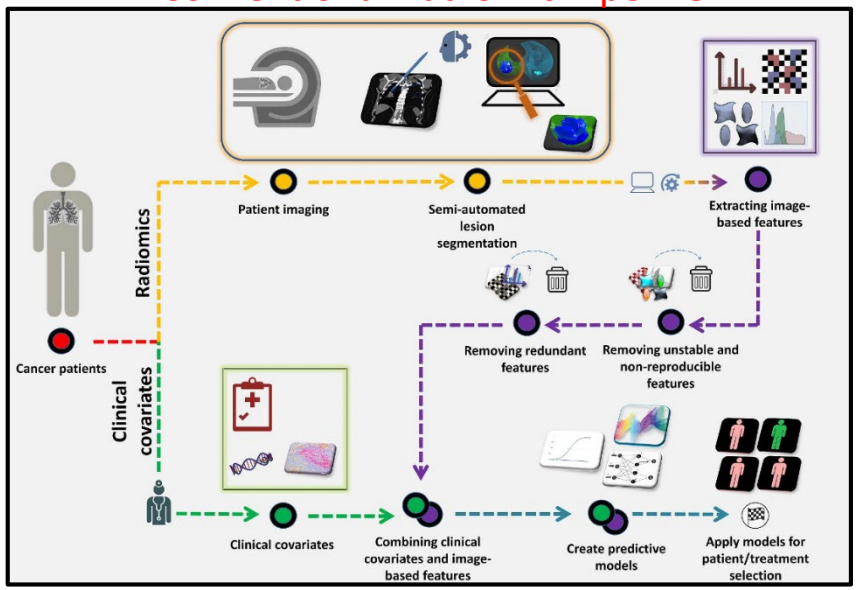
An End-to-End Deep Learning Pipeline

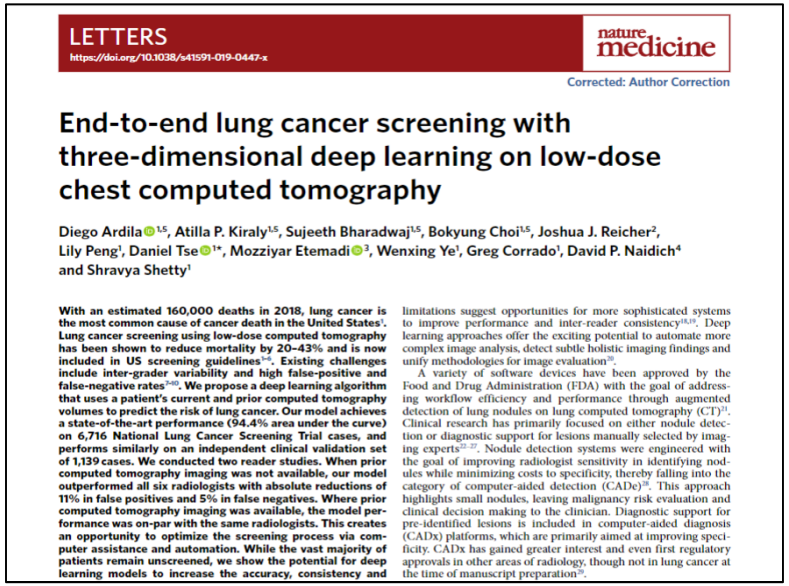
- Conventional radiomic pipelines:
  - **Advantage:** very successful at classifying nodules at the pixel/voxel level
  - **Disadvantage:** Bottlenecks in image curation, image segmentation, feature extraction, QA/QC/analysis

- End-to-End Deep Learning pipeline
  - CT is the input
  - No segmentation needed: Deep Learning does the segmentation and/or input whole volumetric image series
  - Deeply learned classifier algorithms
  - Can easily accommodate 10,000s of images *(See Google)*

- New idea/concept:
  - Develop an end-to-end DL pipeline for IPNs
  - Benchmark against current approaches for reproducibility, stability, portability, and interpretability
  - Long-term goal is to conduct a clinical utility study

Conventional Radiomic 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[1–5]. Existing challenges include inter-grader variability and high false-positive and false-negative rates[2–5]. 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

limitations suggest opportunities for more sophisticated systems to improve performance and inter-reader consistency[18,19]. Deep learning approaches offer the exciting potential to automate more complex image analysis, detect subtle holistic imaging findings and unify methodologies for image evaluation[20].

A variety of software devices have been approved by the Food and Drug Administration (FDA) with the goal of addressing workflow efficiency and performance through augmented detection of lung nodules on lung computed tomography (CT)[21]. Clinical research has primarily focused on either nodule detection or diagnostic support for lesions manually selected by imaging experts[22–27]. Nodule detection systems were engineered with the goal of improving radiologist sensitivity in identifying nodules while minimizing costs to specificity, thereby falling into the category of computer-aided detection (CADe)[28]. This approach highlights small nodules, leaving malignancy risk evaluation and clinical decision making to the clinician. Diagnostic support for pre-identified lesions is included in computer-aided diagnosis (CADx) platforms, which are primarily aimed at improving specificity. CADx has gained greater interest and even first regulatory approvals in other areas of radiology, though not in lung cancer at the time of manuscript preparation[29].

UMB- BRL

Sandy Stass
Feng Jiang
Natalia von Muhlinen


Sandy Stass

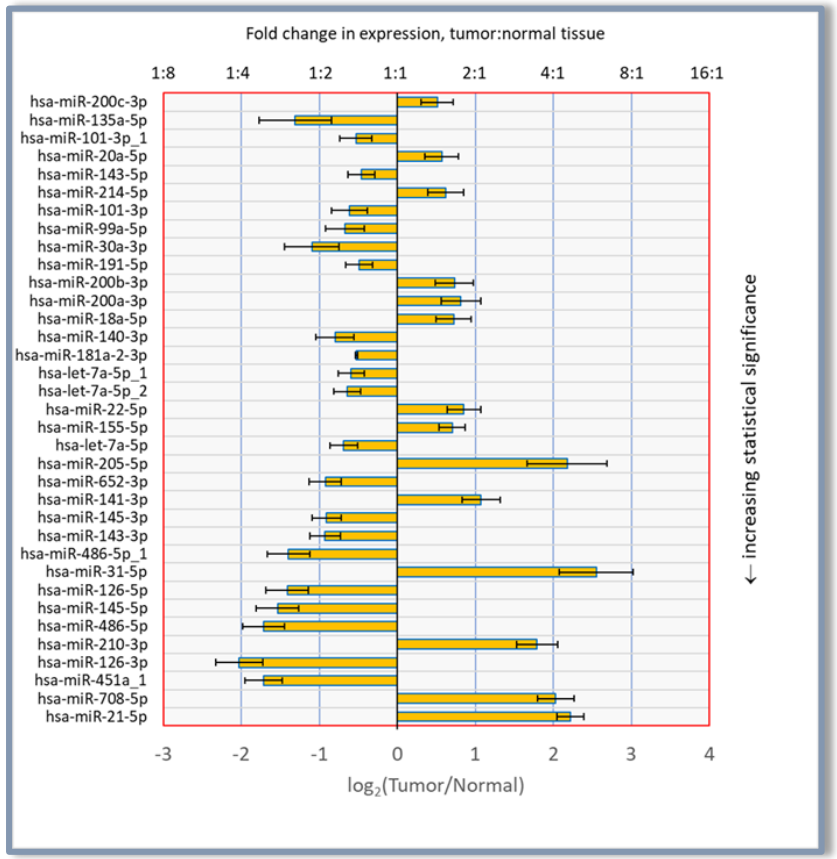

Feng Jiang


Natalia von Muhlinen

miRNA/microbiome-based markers for early detection of lung cancer

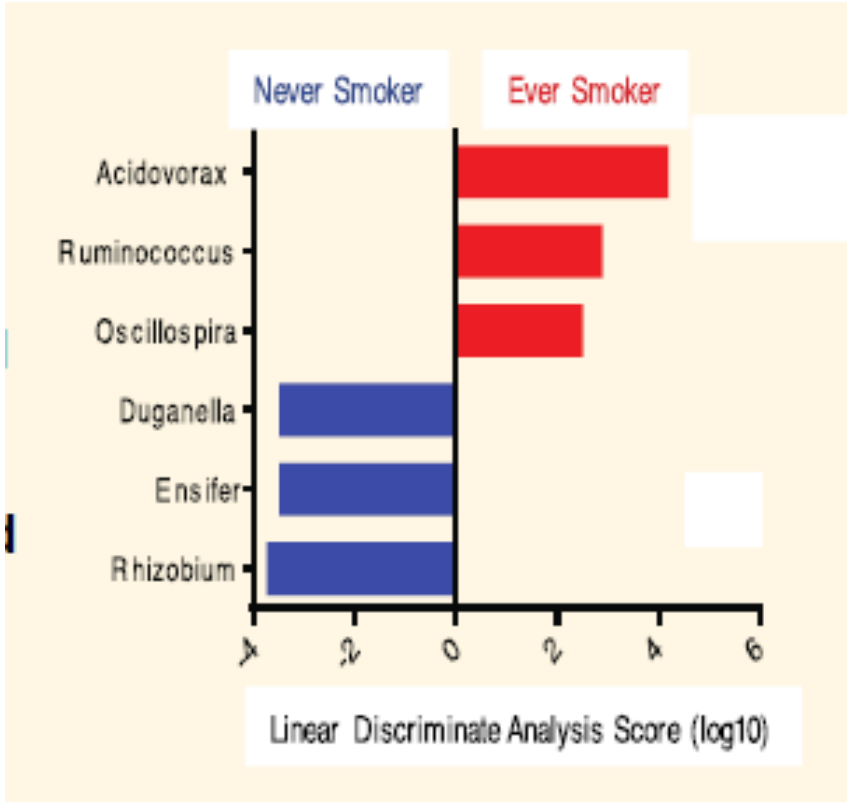
Best Contribution to Science Fiction
Acidovorax

miRNA as Biomarkers for Early Detection of Non-Small Cell Lung Cancer in Sputum
N= 57 NSCLC, 52 CTLS



17 miRNAs
Validation pending into SPUTUM

Acidovorax and other tumor-associated microbes as biomarkers of lung cancer
N=107 cancers



bronchial preneoplastic lesions - normal bronchial tissue- Nasal epithelium

Vanderbilt
CVC

Pierre Massion
Eric Grogan
Steve Deppen
Melinda Aldrich
Chirayu Shah


Pierre Massion


Eric Grogan


Kim Sandler

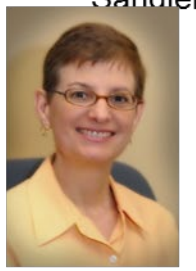

Gary Smith

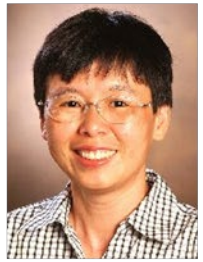

Steve Deppen


Chirayu Shah


Sophie Jouan

Sanja Antic


Rosana Eisenberg


Heidi Chen


Bennett Landman

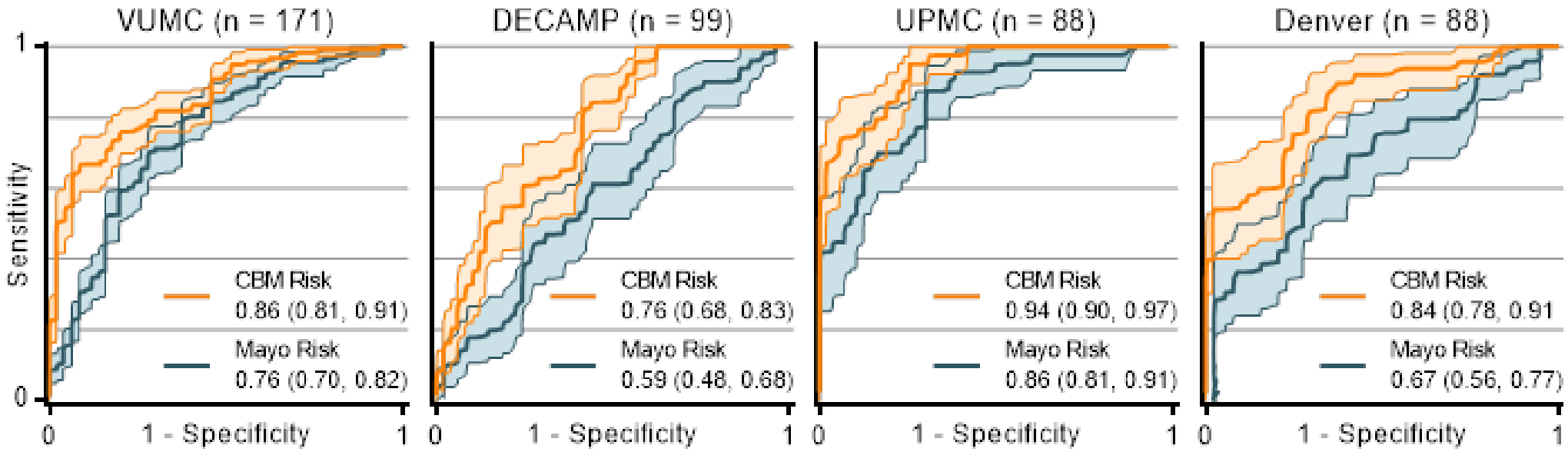

Melinda Aldrich

Best **ENROLLMENT In LTP2** ☺

Management of Indeterminate Pulmonary Nodules

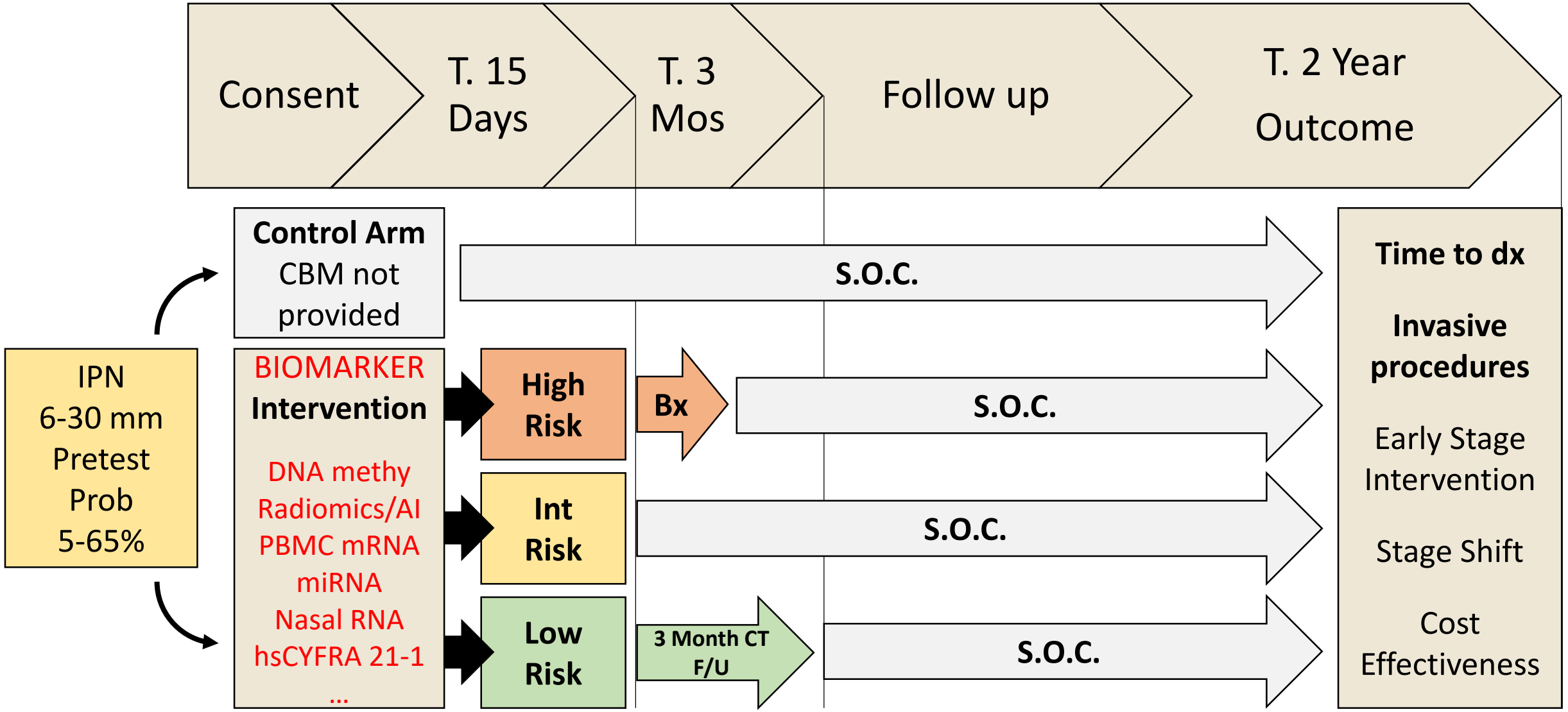
Combined biomarker model in intermediate risk intermediate pulmonary nodules (IPNs)

CBM = Clinical + Radiomics + hsCYFRA 21-1 serum biomarker



Reclassification of ~30% of intermediate risk IPNs

Biomarker driven management of IPN: RCT utility trial



Lung Team project 2 -- LTP2

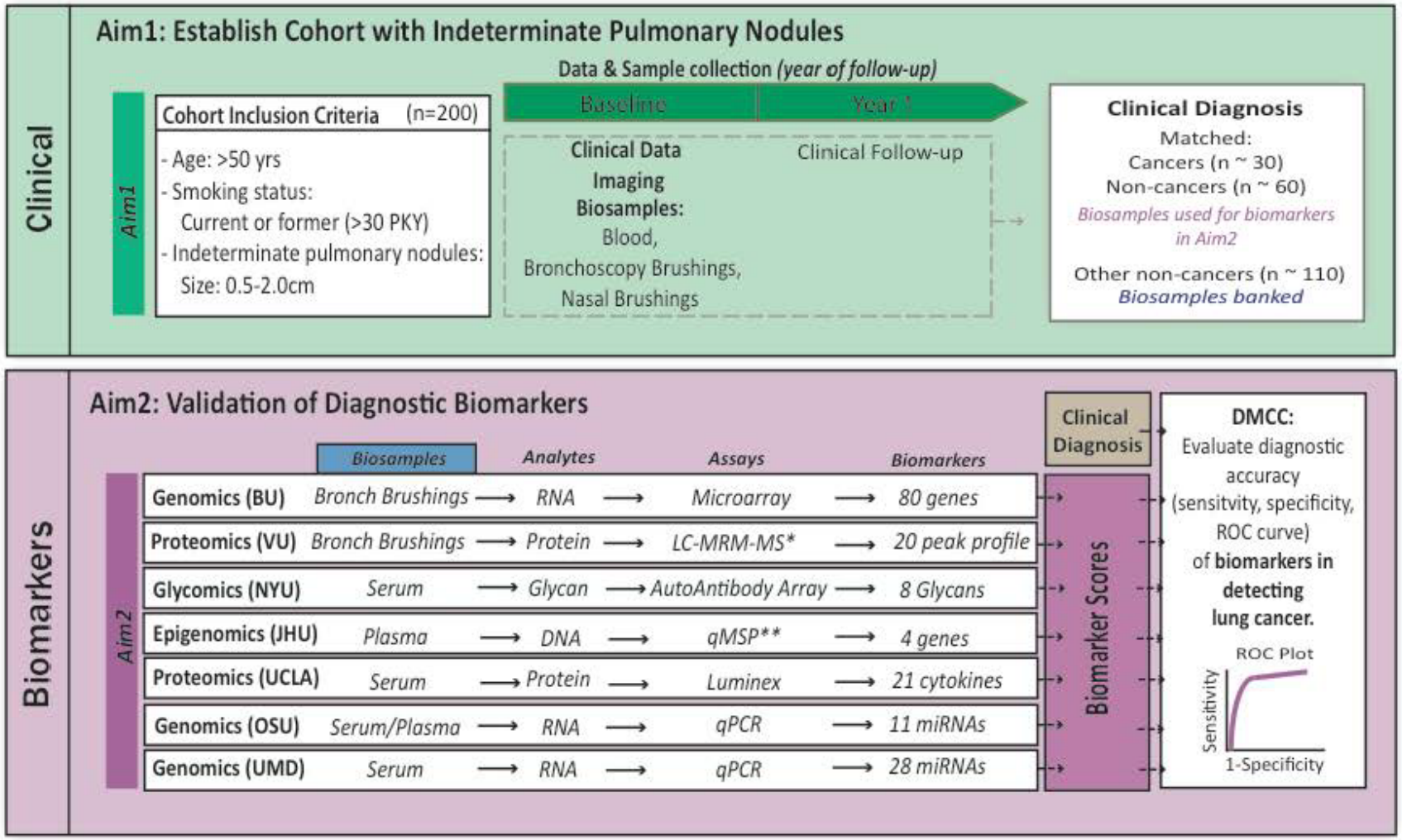


Figure 1: Overview of specific aims.

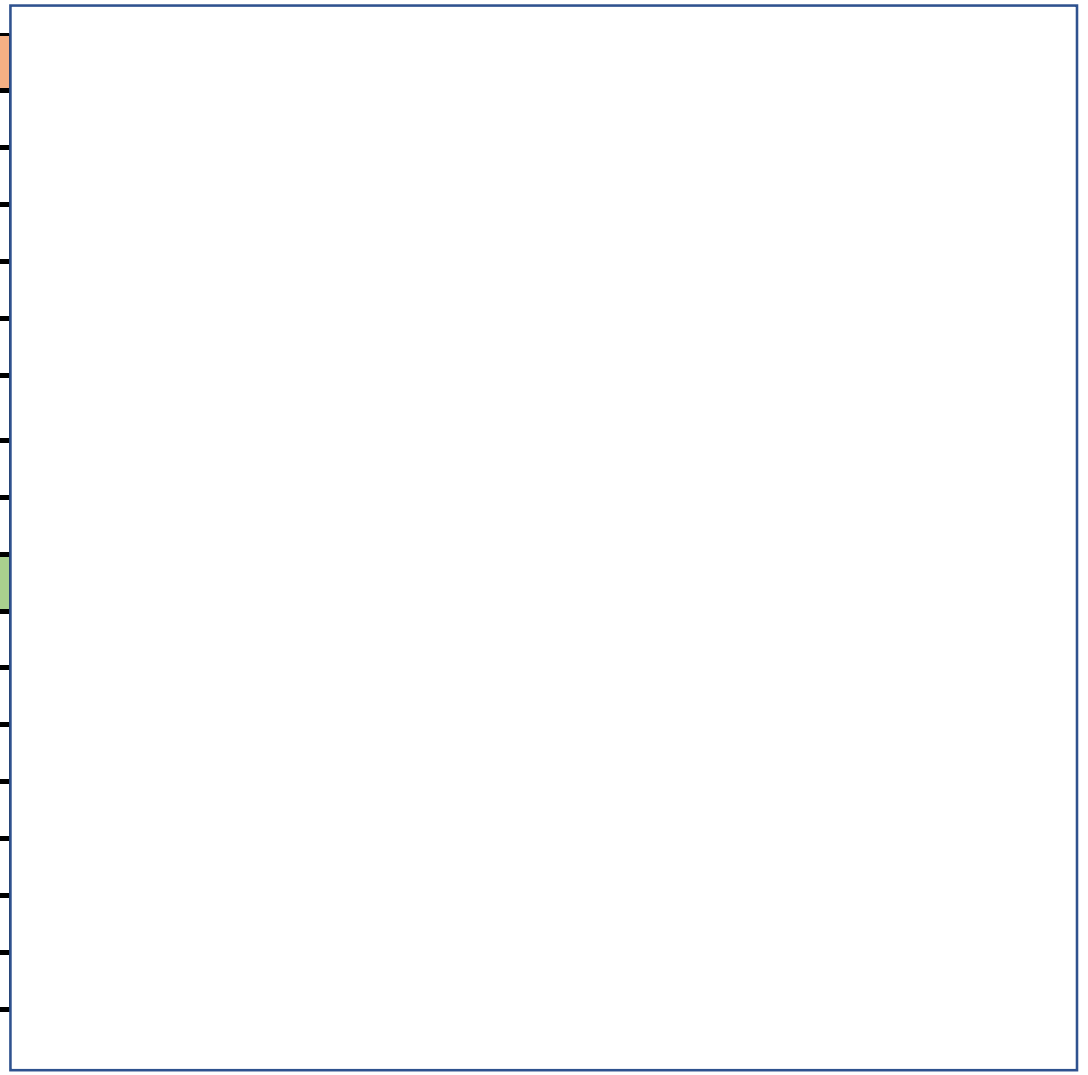
Accural: 261/300
70% cancer prevalence

Biospecimens to NCI/ Frederick

Images repository JPL

SWOT Results

Strengths
BM study design
Use of high-end technologies/ multiple platforms/AI
Rigorous metrics of performance accuracy
Prioritization of Biomarkers
Publications
DMCC biostatistical support
Multi-site collaborations, peer review
Same vision/focus in Biomarker Research
Opportunities
So many
So many
So many
So many
So many
So many
So many



SWOT Results

Opportunities
Clinical utility trials (pragmatic-low cost)
Develop new Cohort studies (never smokers, fam hx..)
Collaborate with other consortia and RO1s, plan ahead
Personalized screening. New eligibility criteria
Data and biospecimen sharing Distributed model/ Master agreements
Build in junior investigators to the application process
Bring advocates to the consortium
Create working groups based on expertise
Career development awards to become associate member
Expanding to other disease outcomes risk stratification for recurrence/response
Rolling cyles of grant applications.
…

Into the future of the EDRN

FOCUS--
Tangible outcomes. Risk -Diagnostics-Stratification for recurrence- Anchoring in Biology
Collaboration with industry USEFUL/ MUTUAL/CLEAR on data use
Including minorities in STUDIES/INVESTIGATORS/SPEAKERS/SCHOLARSHIPS
Engage with other NIH funding programs THEMATIC/ JOINED MEETINGs
Facilitate Accrual COMMUNITY/ USEFUL SAMPLES/TRIAL INNOVATION NETWORK
Role of BRLs reconsidered
Early Phase biomarker clinical TRIALS for UTILITY ANALYSIS
Increase collaborations. GROUP DISCUSSIONS /MONTHLY MEETINGS/ FOCUSED AGENDA
Keep focus on high risk groups NOT READY FOR UNIVERSAL CANCER APPROACH
Detection among NEVER SMOKERS/ Lower risk smokers. Adapting for RACIAL DIFFERENCES
Personalized screening. ADJUSTING eligibility criteria to exposure change