Lung Cancer Detection via Whole-Transcriptome RNA Sequencing of Nasal Epithelium

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PURPOSE

- The goal of lung nodule evaluation is to expedite treatment of malignant nodules and minimize procedures for benign nodules.
- The Percepta Genomic Sequencing Classifier (GSC) is based on the concept of “field of injury”, where altered gene expression is seen in bronchial epithelial cells in current/ prior smokers with malignancy.[1,2]
- This “field of injury” principle has been extended to the nose with evidence that gene expression changes associated with cancer can be detected in the nasal epithelium.[3]
- We report the feasibility of a molecular test developed from non-invasive nasal swab samples for lung cancer detection in current and former smokers.

METHODS

- Swab samples of the nasal epithelium were prospectively collected during the AEGIS I and II clinical trials from current and former smokers with suspected lung cancer lesions found on chest CT.
- Patients were followed for up to one year until a final diagnosis of lung cancer or benign disease was made. Adjudicated Benign and Malignant diagnoses were obtained for each patient.
- A total of 675 subjects were divided into a training set of 411 nasal samples and an independent test set of 261 nasal samples.
- Extracted RNA was analyzed using whole-transcriptome RNA sequencing.[4]
- Sequencing data was analyzed by the Veracyte feature extraction pipeline.
- Machine learning models were developed using gene expression as well as clinical factors such as age, gender, smoking status and nodule characteristics.
- The nasal classifier performance was compared to a clinical risk model (Gould) for risk prediction of malignancy.

CONCLUSIONS

- For Low risk classification, at fixed high sensitivity (96.6%)
  - Clinical genomic classifier achieved overall specificity of ~45%, almost 20 absolute points higher than the Gould model (specificity ~26%)
  - In a population with 25% cancer prevalence, the Nasal Classifier results in over 70% more Benign patients being classified as low risk compared to the Gould model
- For high risk classification, at fixed high specificity (~94%)
  - Clinical genomic classifier achieved overall sensitivity of 50% compared to 42% for Gould model
  - In a population with 25% cancer prevalence, the Nasal Classifier results in over 18% more malignant patients being classified as high risk than the Gould model
- A nasal genomic-clinical classifier developed using whole transcriptome RNA sequencing shows promise in detecting lung-cancer related gene expression changes in nasal swabs from high-risk smokers. Further research is warranted to understand its impact on patient care in a real-world clinical setting.

CLINICAL IMPLICATIONS

A nasal genomic-clinical classifier has the potential to serve as a non-invasive tool for lung cancer risk-stratification among patients with pulmonary nodules.

Training/Independent test set demographic information

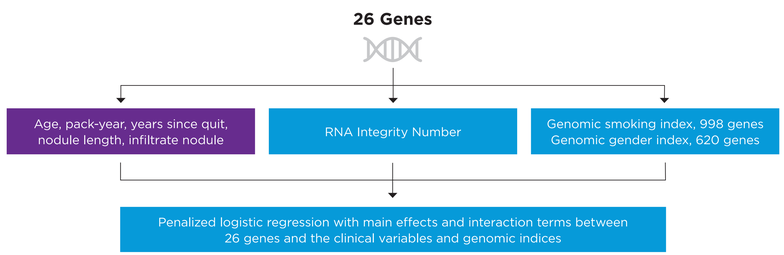
Training Set: 411 patients

Category N=411	Sub-category	Benign 85	Malignant 326
Sex	Male	51	210
	Female	34	116
Age	Median	58	65
Smoking status	Current	25	146
	Former	60	180
Pack-year	Median	30	47
Nodule size (cm)	< 1	9	8
	1 to 2	16	52
	>2 to <3	9	45
	>=3	27	195
	Ill defined infiltrate	20	14
	Unknown	4	12
Nodule location	Central	22	120
	Peripheral	33	90
	Both	26	105
	Unknown	4	11
Histology	SCLC	—	42
	NSCLC	—	250
	Other	—	34
NSCLC type	Adenocarcinoma	—	106
	Squamous	—	100
	Large Cell	—	11
	Other	—	33

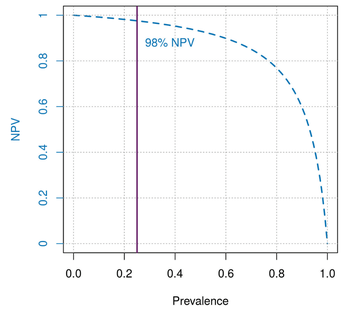
Independent Test Set: 261 patients

Category N=261	Sub-category	Benign 57	Malignant 204
Sex	Male	38	131
	Female	19	73
Age	Median	57	66
Smoking status	Current	23	104
	Former	34	100
Pack-year	Median	20	48
Nodule size (cm)	< 1	7	6
	1 to 2	17	33
	>2 to <3	6	25
	>=3	14	125
	Ill defined infiltrate	10	10
	Unknown	3	5
Nodule location	Central	24	72
	Peripheral	21	61
	Both	8	65
	Unknown	4	6
Histology	SCLC	—	26
	NSCLC	—	161
	Other	—	17
NSCLC type	Adenocarcinoma	—	69
	Squamous	—	62
	Large Cell	—	10
	Other	—	20

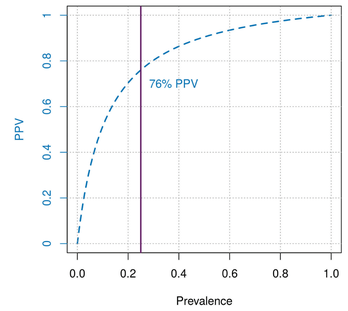
Preliminary Nasal Classifier Combines CLINICAL and GENOMIC Features



The Nasal Classifier performance modeled on a population with 25% cancer prevalence

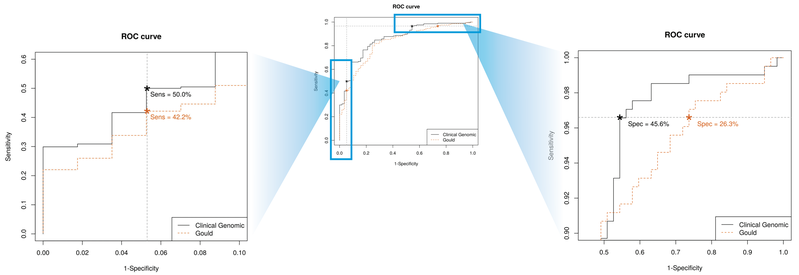


Classification as Low Risk with a specified cut-off
Sensitivity = ~96 %, Specificity = ~45%



Classification as High Risk with a specified cut-off
Sensitivity = ~50%, Specificity = ~94%

Comparison of the Nasal Classifier with a Clinical Model (Gould)



NPV/PPV at 25% prevalence						
	Sensitivity	Specificity	NPV	Sensitivity	Specificity	PPV
Nasal Classifier	96.6%	45.6%	97.6% [94.8 – 98.9]	50.0%	94.7%	76.0% [51.1 – 90.6]
Gould	96.6%	26.3%	95.8% [90.8 – 98.2]	42.2%	94.7%	72.8% [46.7 – 89.0]

Initial Independent Test Set Performance using the Nasal Classifier with one cut-off

Incoming Suspicious Nodules	Sensitivity	Specificity
All (N=261)	**96.6%** [93.1 – 98.6]	**45.6%** [32.4 – 59.3]

Subsequent Independent Test Set Performance using Classifier with two cut-offs

Sensitivity > 96% for Classification as Low Risk

Incoming Suspicious Nodules	Sensitivity	Specificity
All (N=261)	**96.6%** [93.1 – 98.6]	45.6% [32.4 – 59.3]

Specificity > 94% for Classification as High Risk

Incoming Suspicious Nodules	Sensitivity	Specificity
All (N=261)	50.0% [42.9 – 57.1]	**94.7%** [85.4 – 98.9]

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