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Physiological measures as biomarkers of COPD onset

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World Companion Diagnostics Summit, Frankfurt, April 23-24

What is COPD?

COPD = **C**hronic **O**bstructive **P**ulmonary **D**isease

Disease Pathology	Clinical Symptoms
Emphysema	• Breathlessness • Lower levels of Oxygen in the blood • Collapsed smaller airways • Airway Crackling, air trapping • Time to exhale longer than time to inhale
Chronic Bronchitis	• Chronic Cough • Excess Mucus production and non-clearance • Persistent exacerbating infections • Wheezing • Bronchiectasis (dilated and collapsible bronchi)
Small Airway Fibrosis	• Decreased ability to exhale and inhale • Reduction in FEV_1 which is non-reversible

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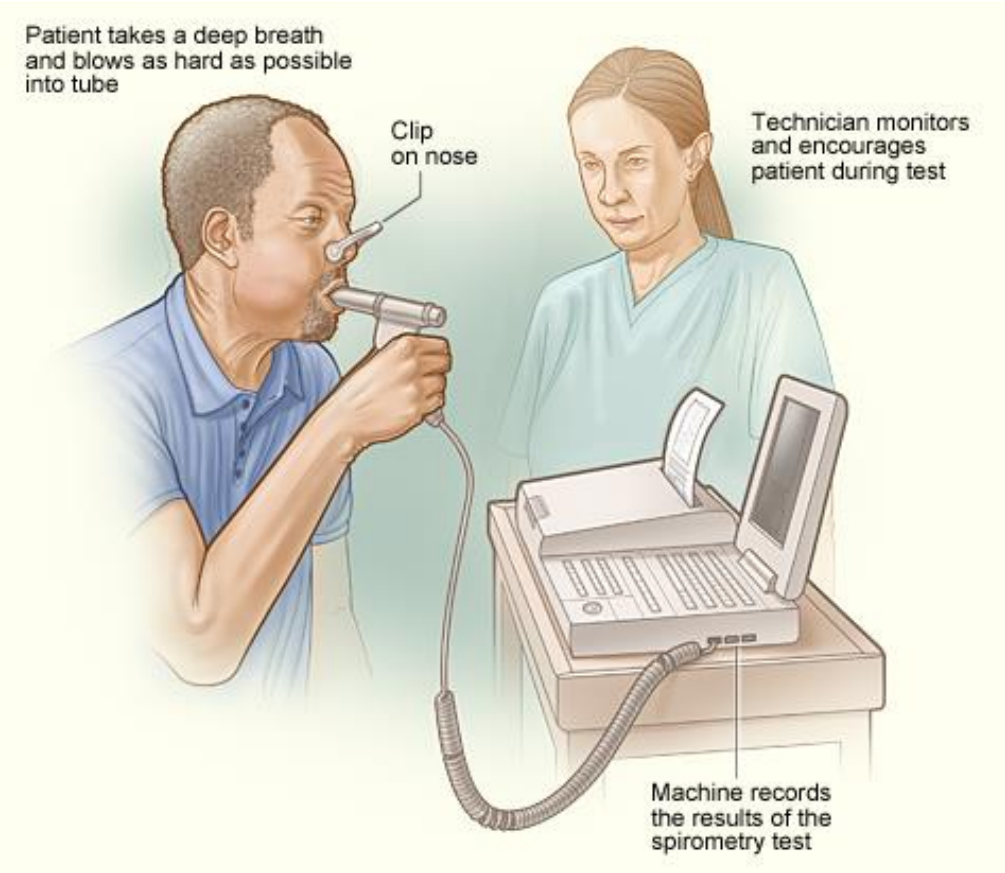
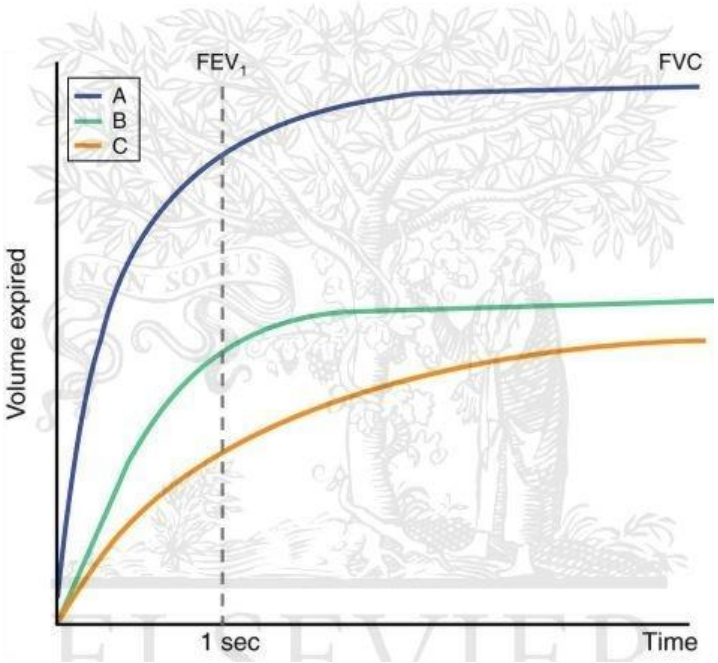
Spirometry

FEV_1 = **F**orced **E**xpiratory **V**olume in **1** sec

FVC = **F**orced **V**ital **C**apacity





http://www.nhlbi.nih.gov/health/health-topics/topics/copd/diagnosis.html

http://www.elsevierimages.com/image/26051.htm

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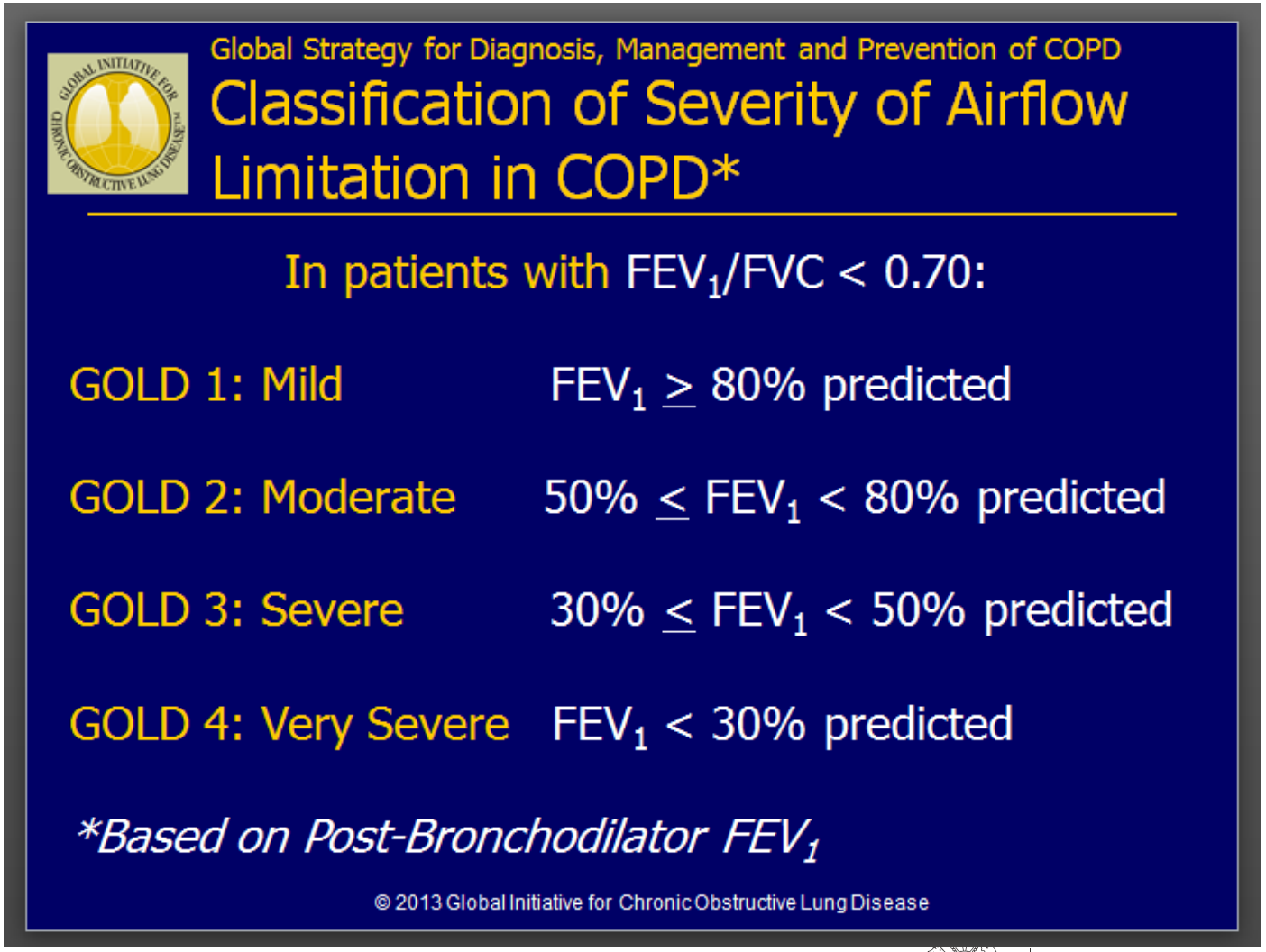
How is COPD diagnosed?



What are biomarkers of COPD onset?

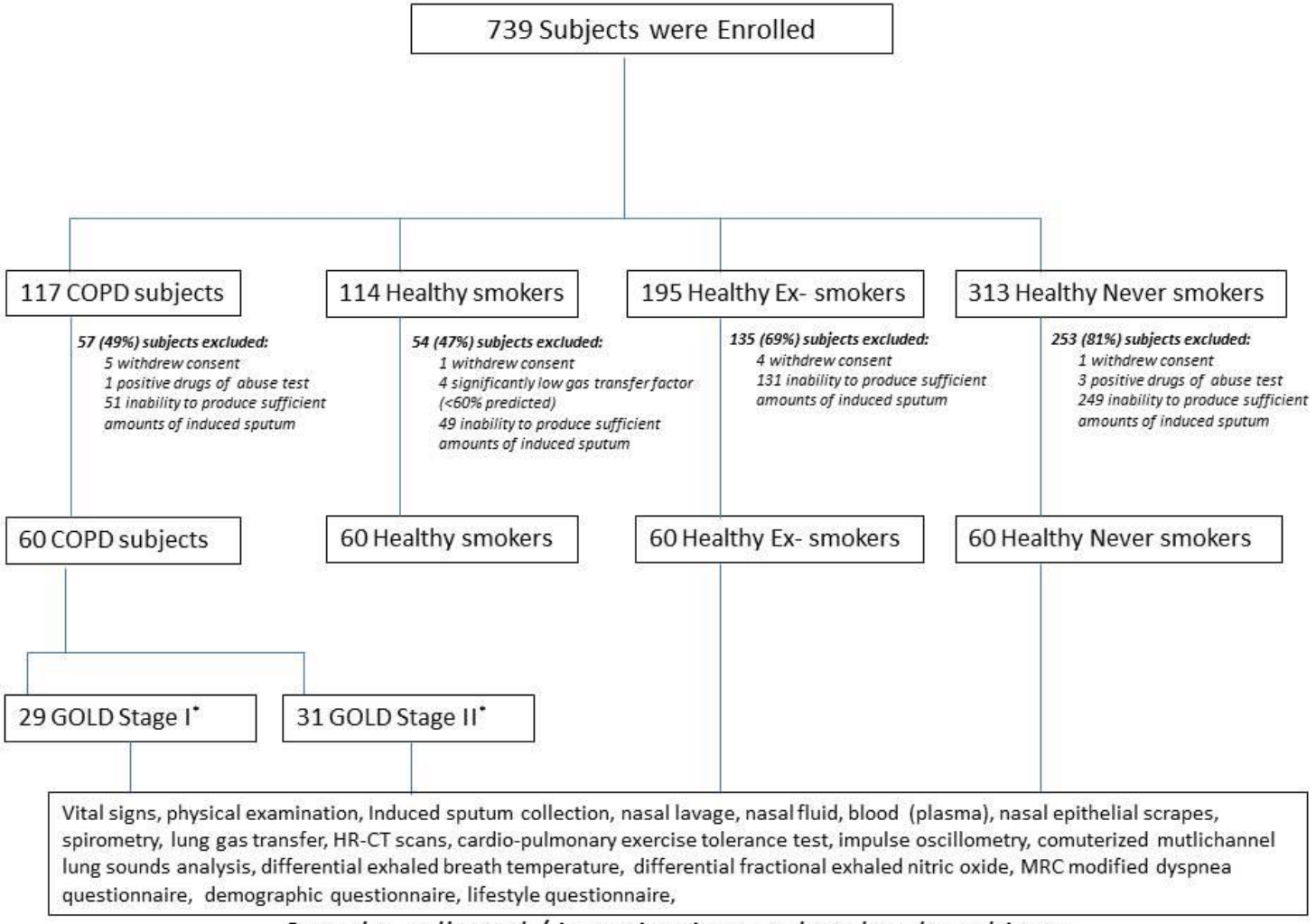
- Chronic Obstructive Pulmonary Disease (COPD) is primarily caused by cigarette smoking
- The aim for PMI is to commercialize a Reduced Risk Product (RRP)* which cigarette smokers can switch to and which reduces the risk of developing smoking related diseases, including COPD
- COPD takes 20-25 years of habitual smoking before it develops. Assessment of any product would therefore take 20-25 years in order to have an assessment comparative to cigarette consumption.
- Can we determine the biological processes (the biological networks) which are perturbed during smoking, which eventually lead to the development of COPD?
- Can these biological network perturbations be monitored with molecular or physiological markers?

RRP is the term we use to refer to products that have the potential to reduce individual risk and population harm

Objectives of Study

- The objective of the study was to identify potential biomarkers that could be further validated in subsequent studies as Biomarkers of COPD onset
- Physiological and molecular biomarkers were considered
- Identified biomarkers which would be considered for further validation were required to fulfil the following characteristics:
  - Differential levels between Never-smokers and Healthy Smokers, with reversibility in the Ex-smokers
  - Differential levels between COPD and Healthy Smokers
- The eventual aim of this study is to identify a panel of biomarkers which can go through a future validation process

A study to identify biomarkers of COPD onset



Samples collected / investigations undertaken by subjects

*GOLD stage as defined by the GOLD Guidelines 2009

ClinicalTrials.gov study identifier: NCT01780298

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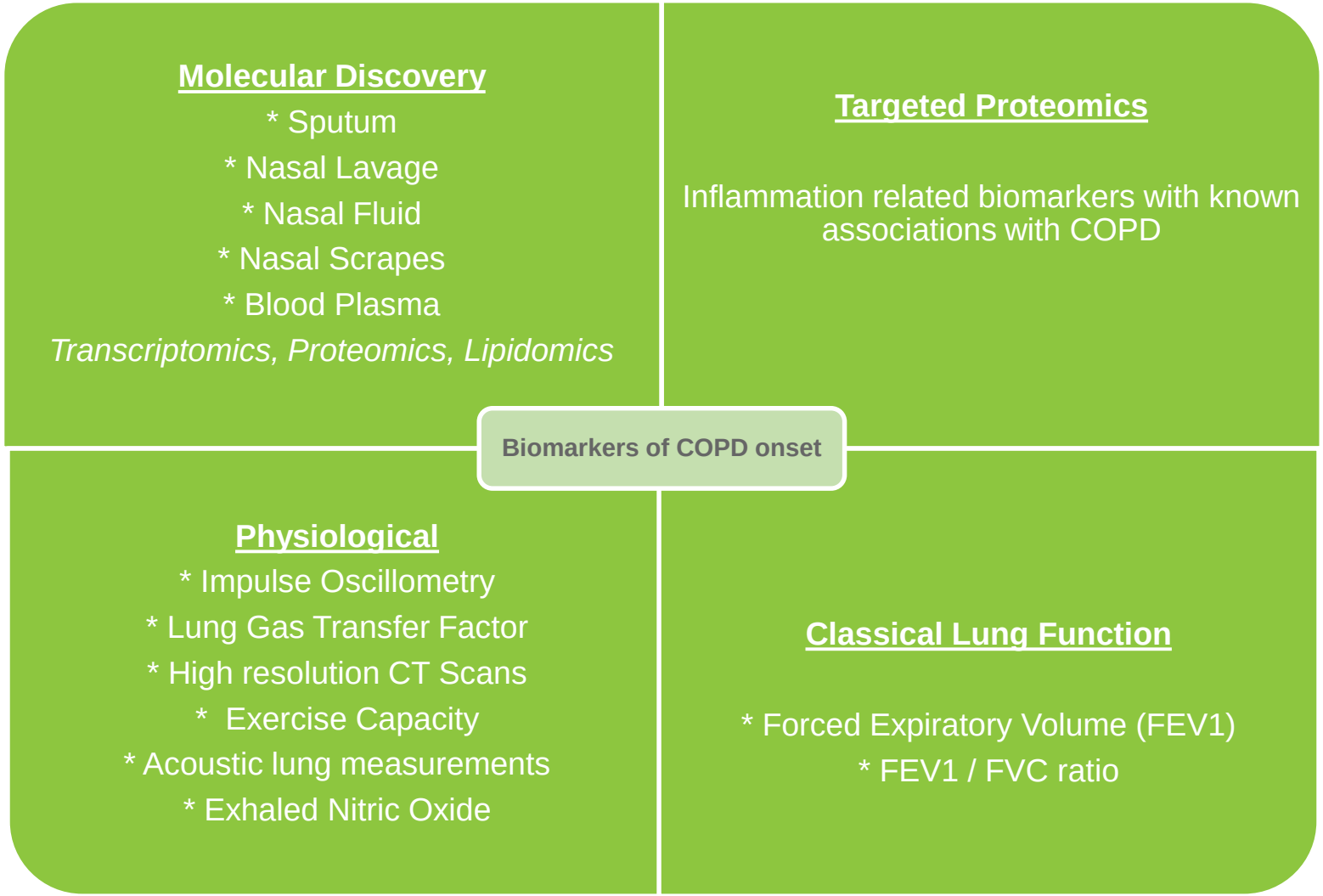
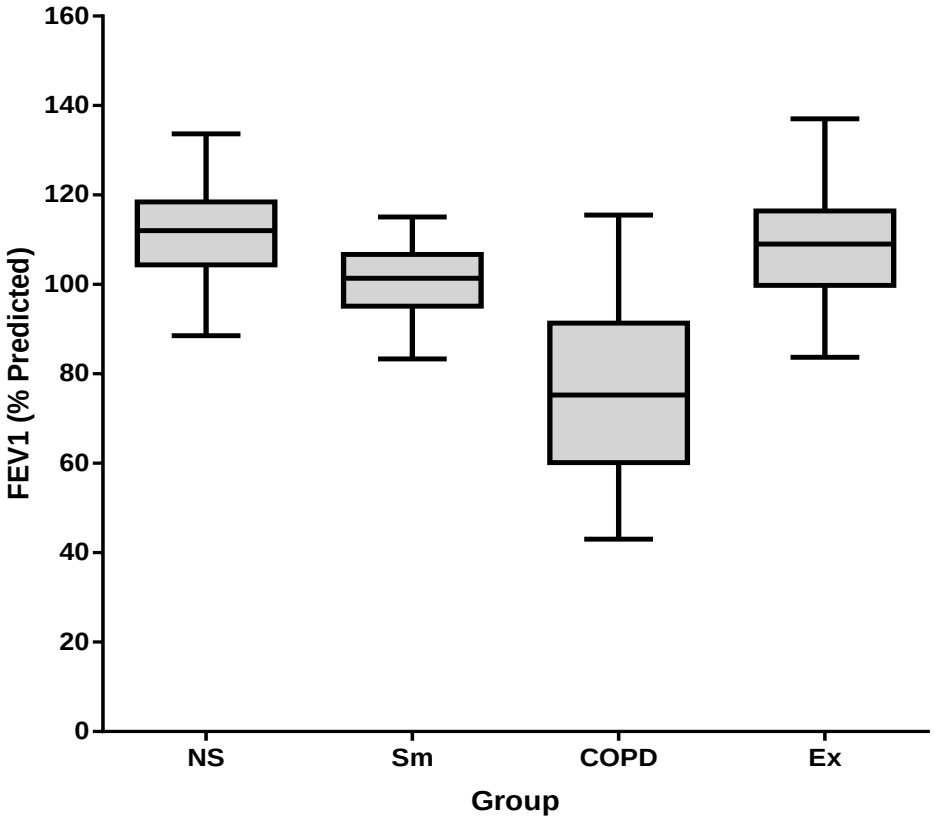
A study to identify biomarkers of COPD onset

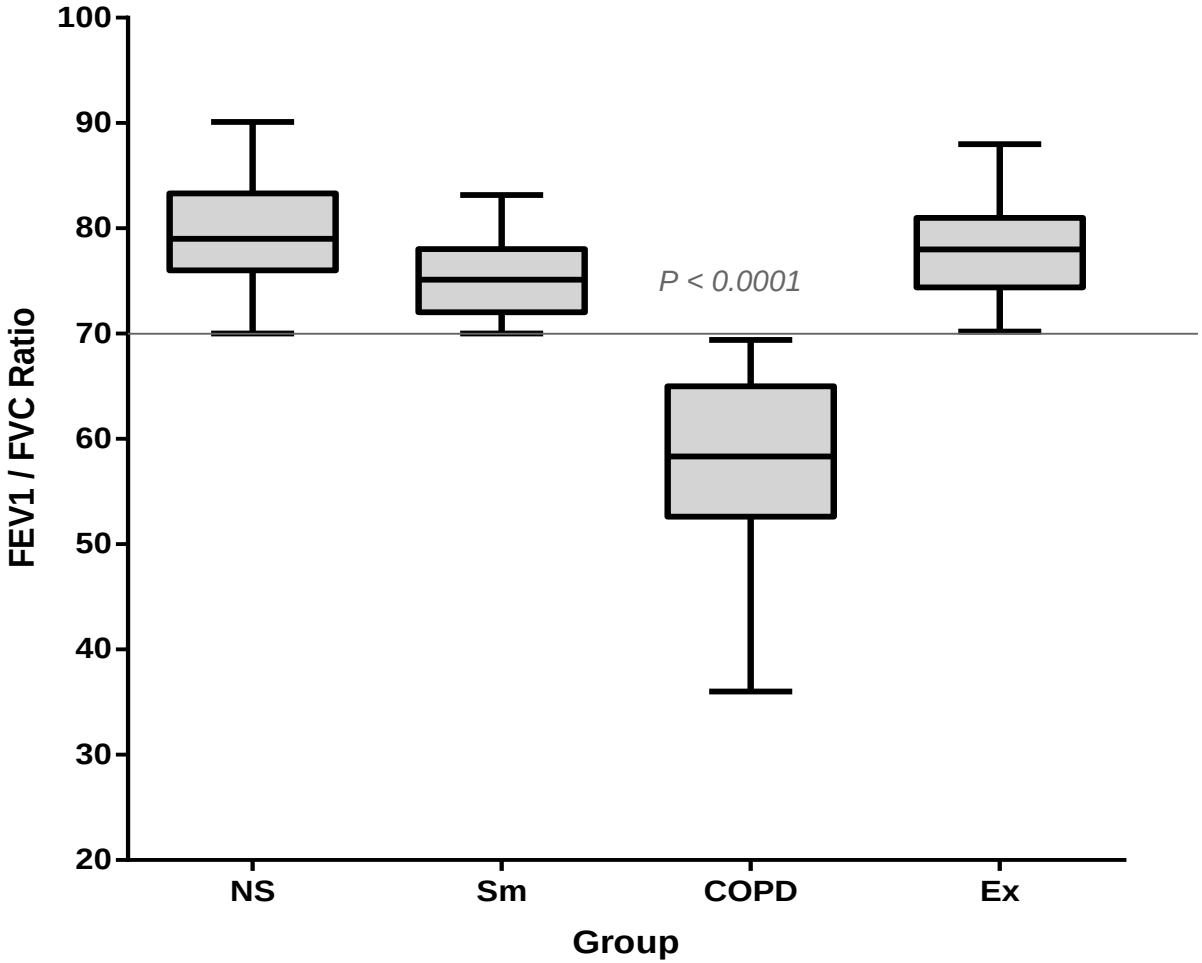


Non-Molecular Results

FEV_1 (Forced Expiratory Volume in 1 sec)



FEV_1/FVC ratio



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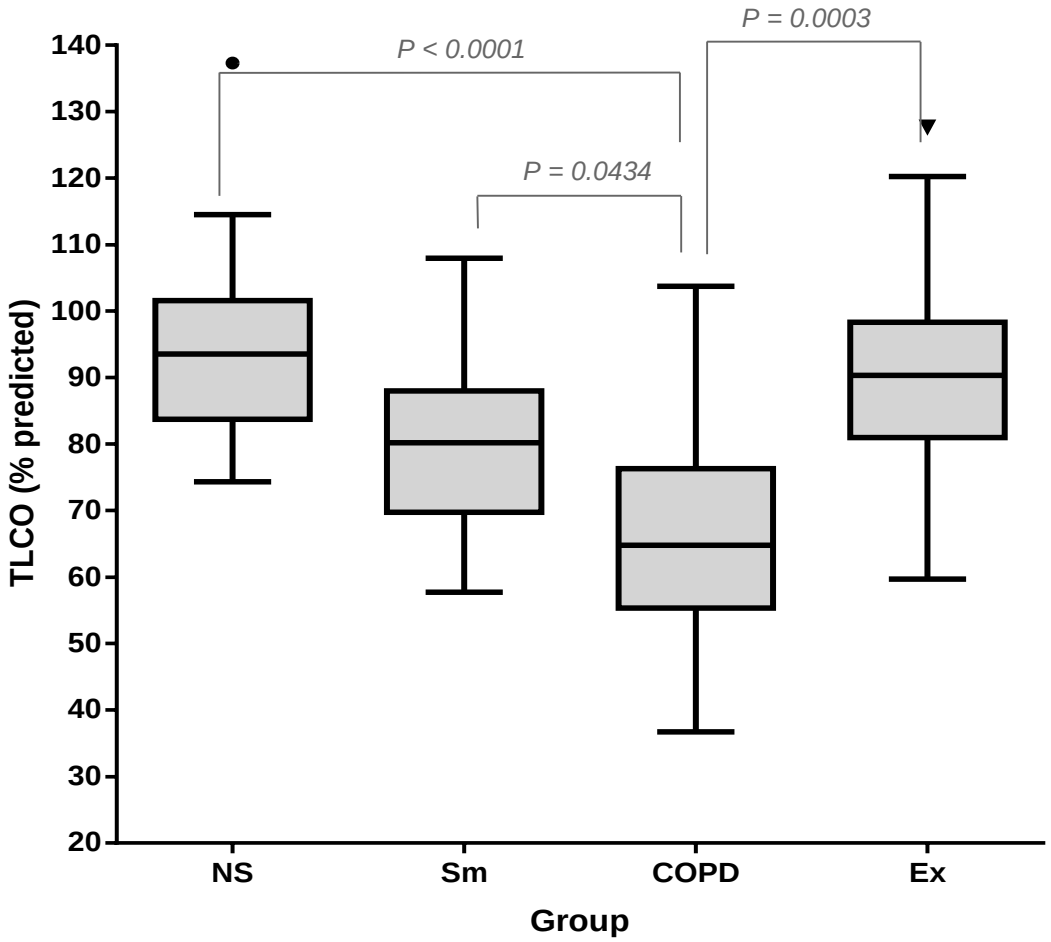
Transfer Factor (TLCO) % Predicted



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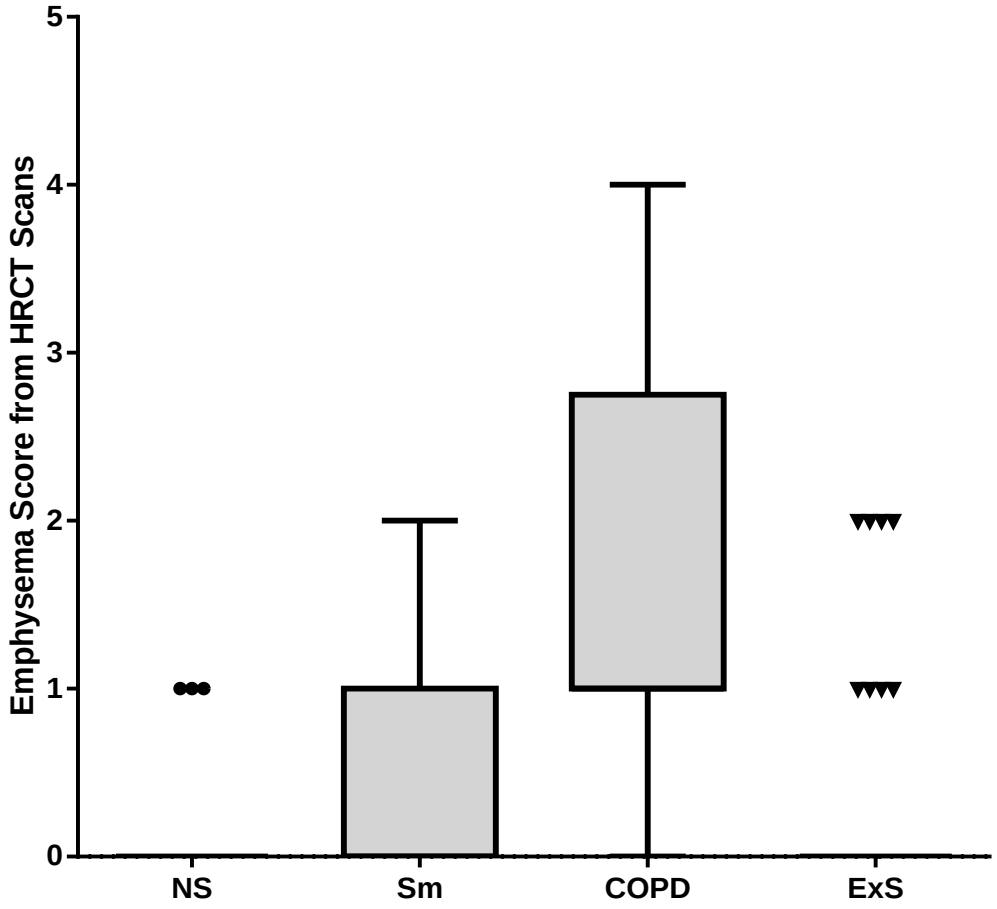
Emphysema Index from HRCT scans



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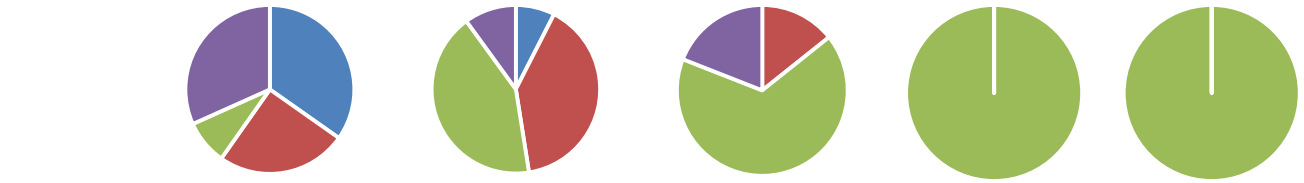
The Table of Representatives

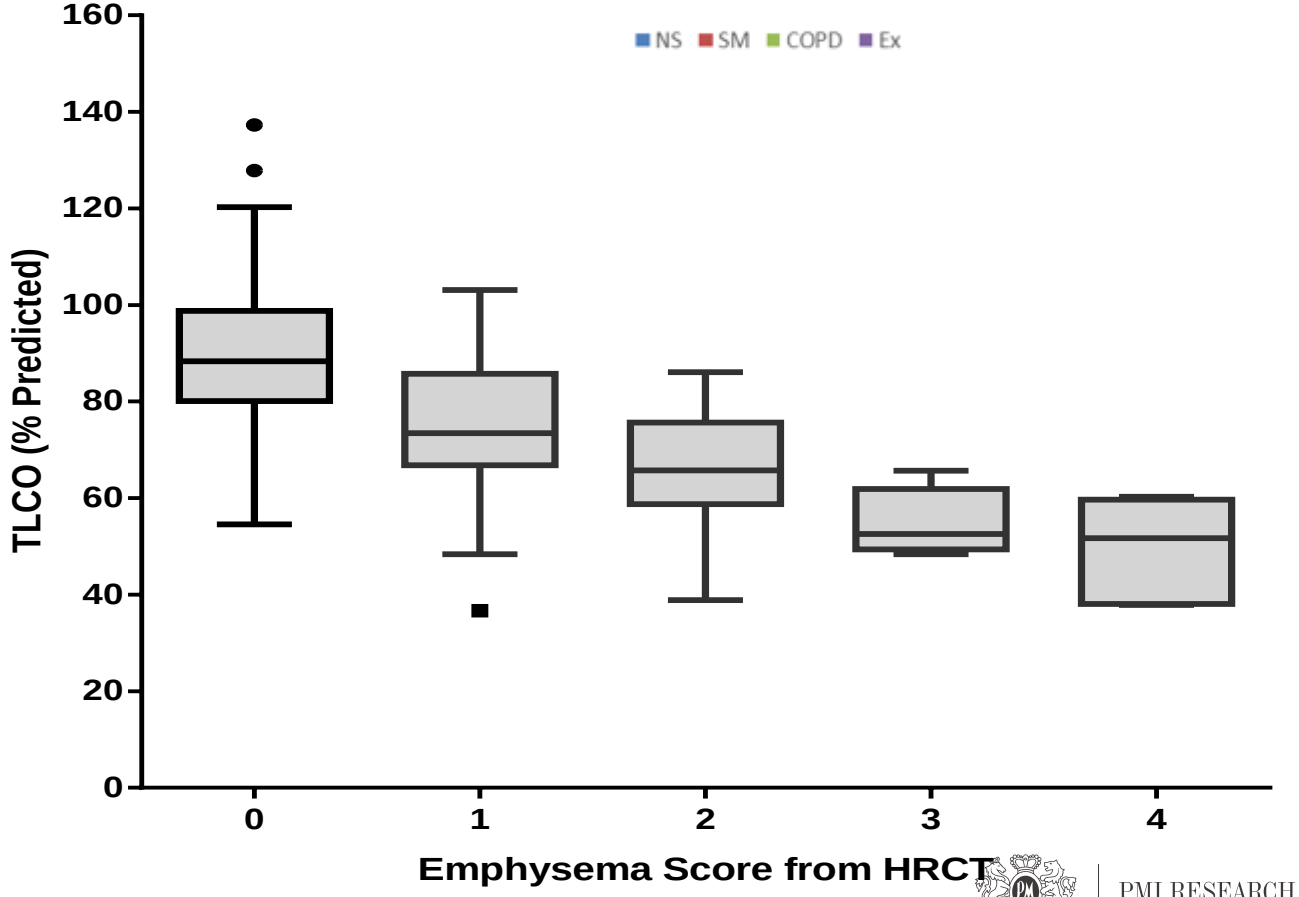
Subject	COPD	HS	HExS	HNS
Gender	F	F	F	F
Age	60	55	58	58
FEV1 % Predicted	73%	100%	116%	98.2%
FEV1/FVC ratio	0.462	0.76	0.81	0.86
TLCO % of predicted	37.5%	74.2%	75%	83%
VO2 % of predicted	70%	86%	105%	79%
Emphysema Score on HRCT	4/4	2/4	1/4	0/4
HRCT Extent of disease score	4/4	2/4	1/4	0/4
mBODE Score	4/5	1/5	1/5	2/5

The Table of Interesting "Healthy" Smokers

Subject	S 1	S 2	S 3	ExS 1
Gender	M	M	M	F
Age	45	68	60	64
FEV1 % Predicted	105.6%	115%	119%	106%
FEV1/FVC ratio	0.75	0.78	0.75	0.73
TLCO % of predicted	65 %	68%	104%	74 %
VO2 % of predicted	74 %	61%	81 %	116 %
Emphysema Score on HRCT	2/4	0/4	0/4	2/4
HRCT Extent of disease score	2/4	3/4	3/4	2/4
mBODE Score	1/5	3/5	1/5	1/5

Emphysema Score from HRCT scans against transfer factor





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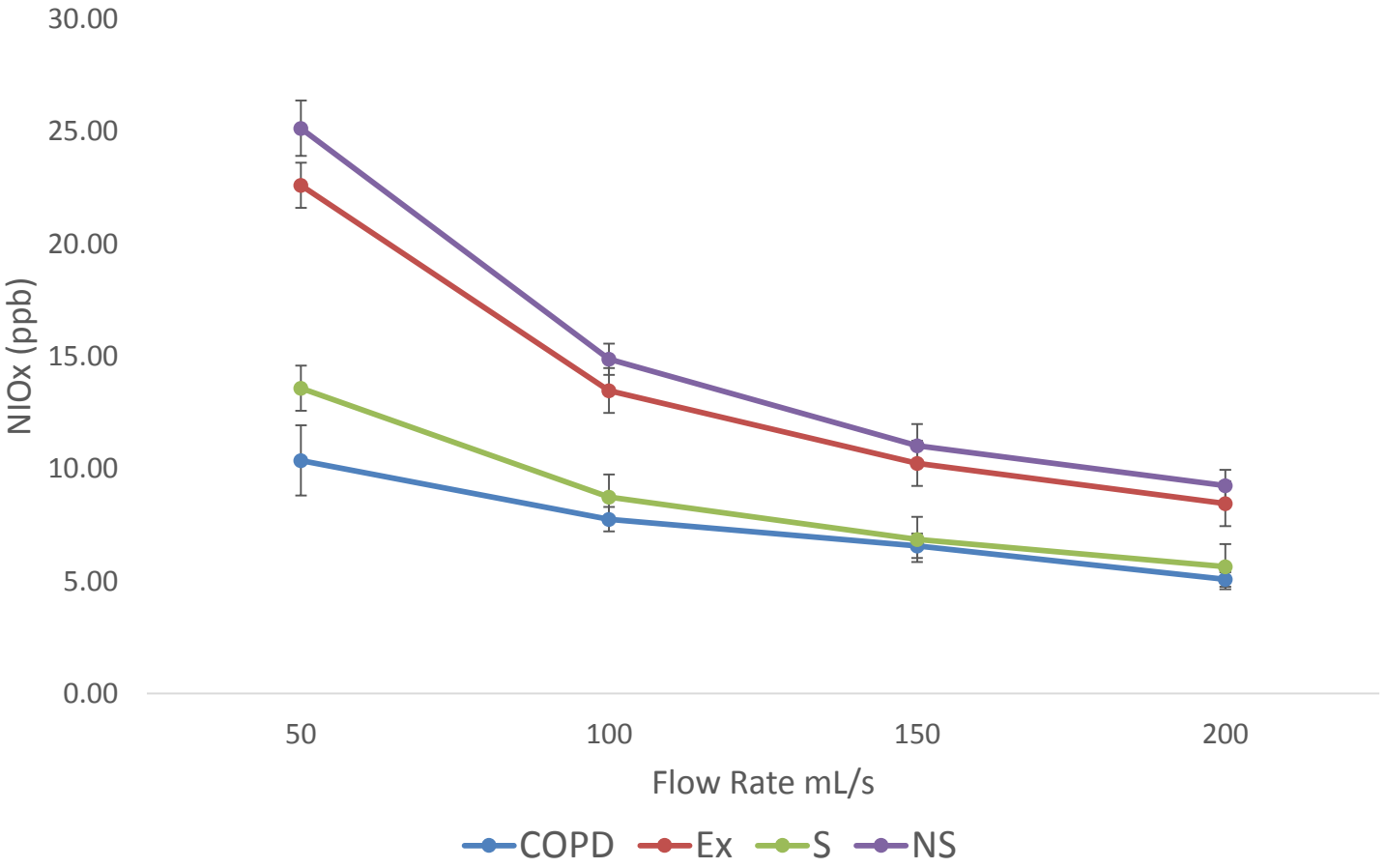
Differential Flow-Exhaled Nitric Oxide



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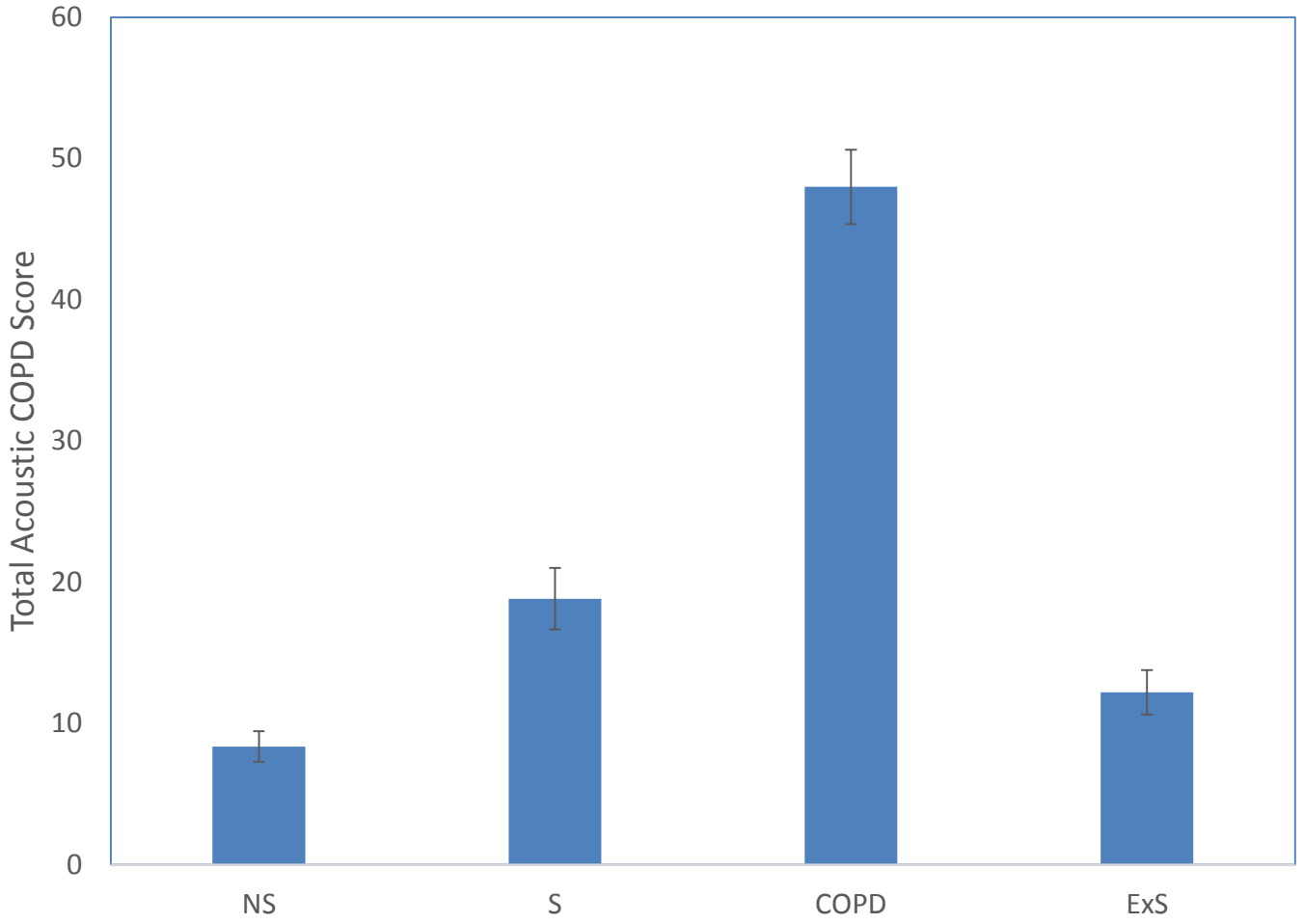
Stethographics COPD Score



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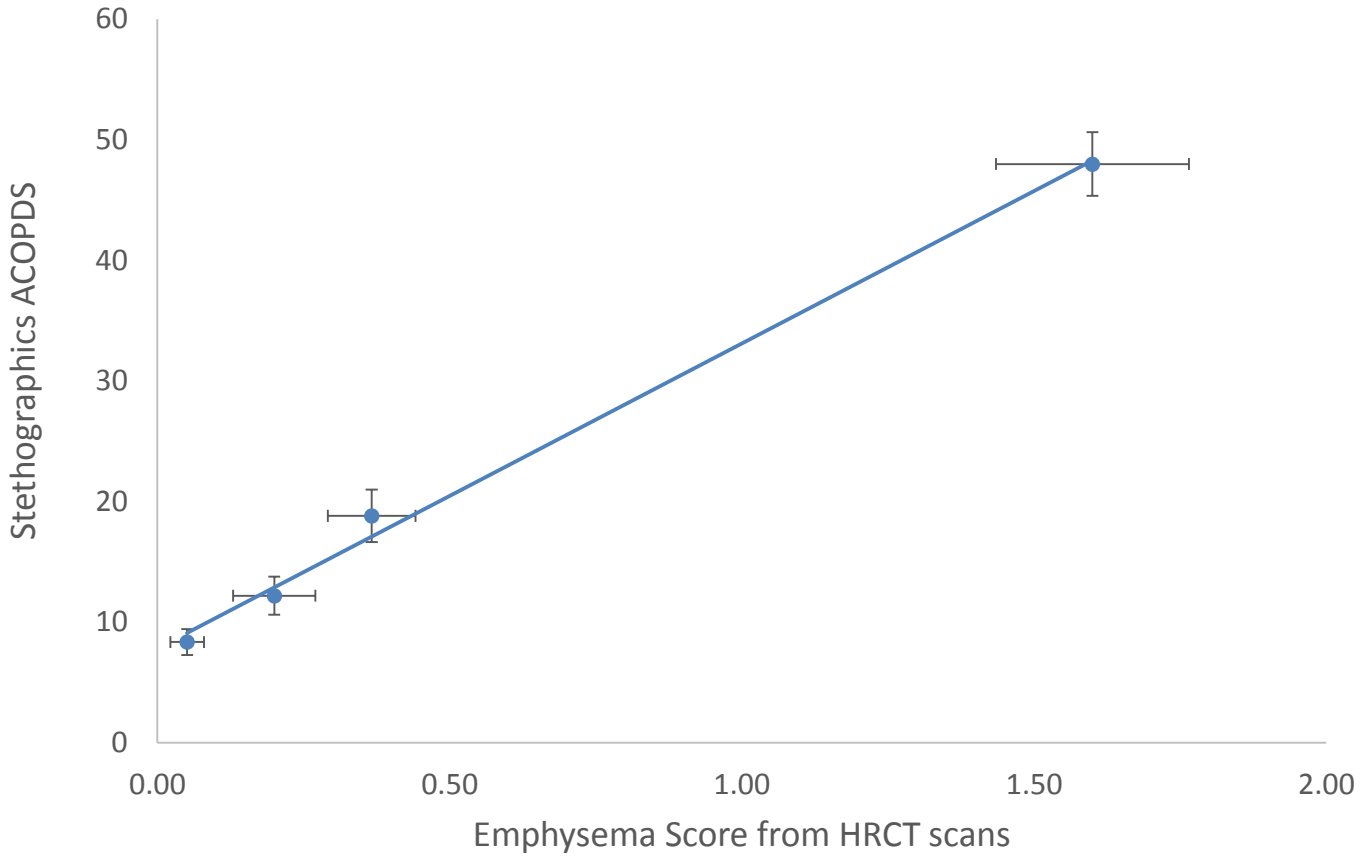
Stethographics COPD Score v HRCT COPD Score



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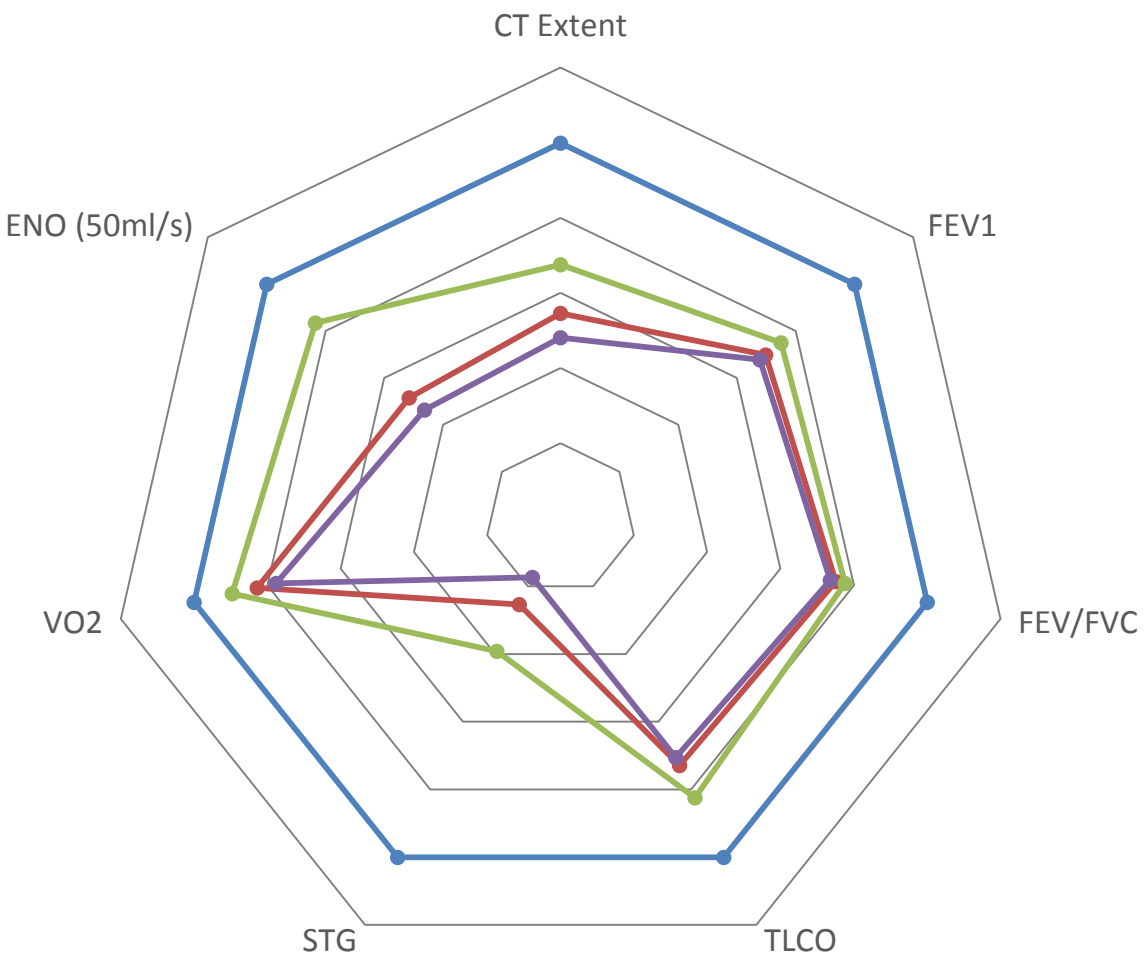
Conclusion:
Integration of physiological parameters as a biomarker

COPD Healthy Smokers Ex-smokers Never Smokers



1. **CT Extent**: Extent of disease score as assessed by radiographer
2. **ENO**: Exhaled Nitric Oxide at flow rate of 50mL/s
3. **VO2**: Maximal oxygen uptake
4. **STG**: Stethographics multichannel lung sound analysis score
5. **TLCO**: Lung Transfer Factor
6. **FEV1/FVC:** Ratio of FEV1/FVC. % of predicted
7. **FEV1**: Forced Expiratory Volume in 1 sec. % of predicted

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Summary

1. **There are a number of physiological biomarkers that have previously been shown to correlate with COPD severity, that show promise as biomarkers of COPD onset**
   - *i.e. They are altered (higher or lower) in healthy smokers compared to never-smokers and they return to "near-normal" levels in ex-smokers*
2. **The traditional way of diagnosing COPD, maybe too blunt to identify smoking subjects that have some pathology demonstrating the "very early" stages of COPD**
   - *i.e. Many smoking subjects with normal FEV1 and FEV1 /FVC ratio show signs of significantly pathology using HRCT, Stethographics and Transfer Factor measurements*
3. **There is further understanding to be gained by analyzing the results of the physiological measures and molecular biomarkers by correlation with Transfer Factor or HRCT scores rather than the traditional FEV1 .**
   - *i.e. stratification of subjects by criteria other than FEV1 is more likely to provide further understanding of the very early disease processes that lead to the development of COPD*

Summary

5. Currently Transcriptomics and Proteomics analysis is being completed.

- *The results will be correlated with FEV_1 and other physiological measurements to understand if molecular signatures can describe the early pathophysiological changes that can be detected in what appear to be healthy individuals*

6**. The assessment approach for RRPs can not rely solely on traditional methods in which diseases are diagnosed or monitored**

- *A more comprehensive battery of tests gives a more sensitive determination of airway health and is likely to be better suited to understanding pre-symptomatic changes that occur in lung health*
- *The combination of a battery of physiological markers with molecular markers may provide even more sensitivity to identify such changes.*

Acknowledgements

- Many thanks to the following colleagues for making this study possible :

Filippo Toni – *Project Management*

Jeremie De Torrente – *Project Management*

Mary-Anne Kedda – *Study Initiation*

Kishor Lad – *Data Management*

Patrick Picavet – *Medical Safety Officer*

All the clinical staff at QASMC, London, UK.