

Harm Reduction Substantiation: Challenges and Opportunities



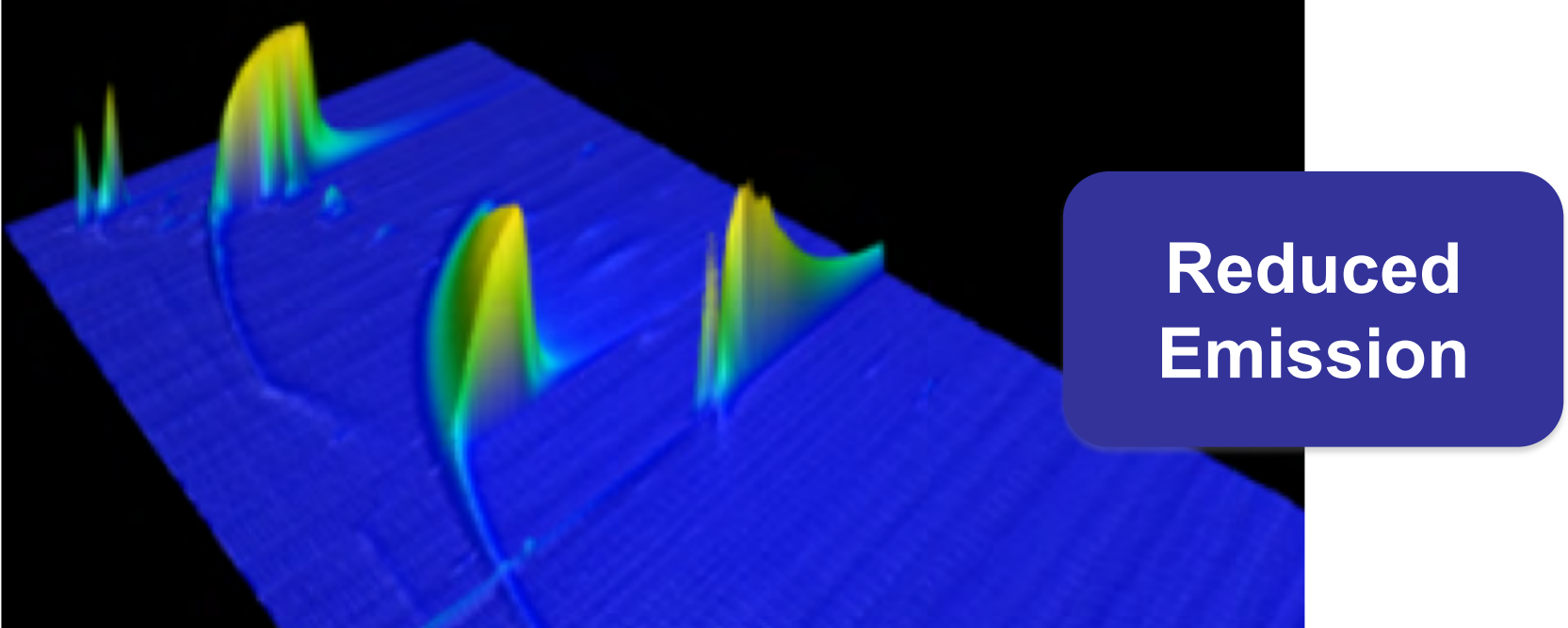
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Università di Catania – ITALY



?

Reduced Risk/Harm

Reduced Exposure



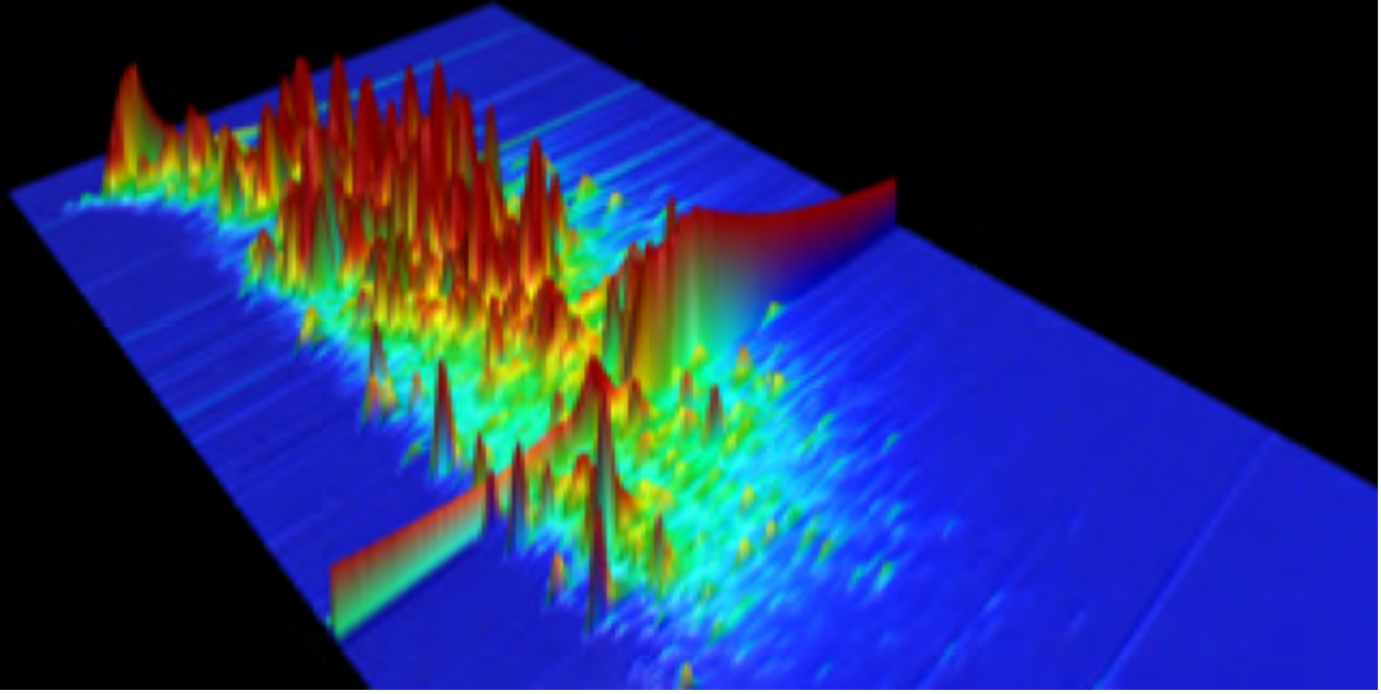
Reduced Emission

≈ 200 chemicals in EC/HTP aerosol

COMBUSTION-FREE



Smoking-related diseases



> 8000 chemicals in tobacco smoke

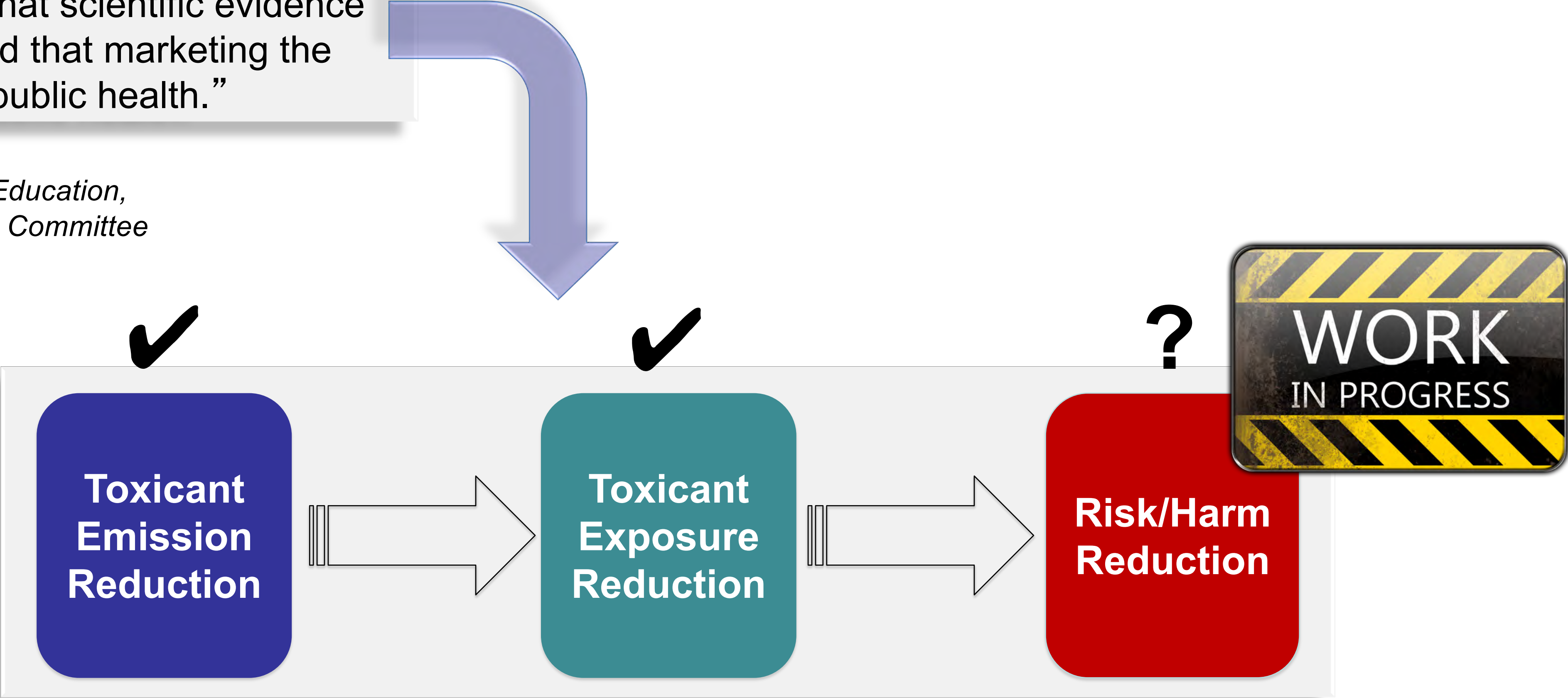
COMBUSTION



Scientific Evidence Must Support Decision Making

- “...direct and implied claims of reduced risk only if FDA confirms that scientific evidence supports the claim and that marketing the product will promote public health.”

*Mitch Zeller
US Senate Health, Education,
Labor and Pensions Committee
May 2014*



Substantiation framework for combustion-free tobacco products

Substantiation of risk reduction and harm reversal



Risk/Harm
Reduction

Evidence to prove the health impact of C-F products....

- Epidemiology
- Clinical studies (health effects indicators, biomarkers of potential harm)

IM - ORIGINAL



Changes in biomarkers after 180 days of tobacco heating product use: a randomised trial

Nathan Gale¹ · Michael McEwan¹ · Oscar M. Camacho¹ · George Hardie¹ · Christopher J. Proctor² · James Murphy³

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Disease Relevant BoPHs for Switching Studies



HDL-C

WBC

sICAM-1

11-DTX-B2

8-epi-PGF2 α

The quest for useful health effect indicators

Internal and Emergency Medicine
<https://doi.org/10.1007/s11739-021-02837-2>

IM - COMMENTARY



Examining the evidence for the health impact of combustion-free products: progress and prospects for tobacco harm reversal and reduction

Riccardo Polosa^{1,2,3}

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Lack of early and clinically significant endpoints

Focus on health effect indicators that are specifically relevant to smoking cessation and switching studies

Accelerate discovery science (validation of promising novel candidates).

Study endpoints for substantiation of health-focused MRTTP claim

Urine

- 8-epi-prostaglandin F2 α Type III
-

Patient-reported outcomes

- Smoking Cessation Quality of Life
- Other questionnaires

Blood

- White blood cell count
- s-ICAM1
- hsCRP
- Plasminogen activator inhibitor-1
- Endothelin-1
- Total cholesterol, HDL, LDL
-

Physiological Measures

- Blood pressure
- Spirometry (including FEF25-75%), impulse oscillometry
- Augmentation Index, pulse wave velocity
- 6-minute walking test
- VO₂max
- Saccharin test
-

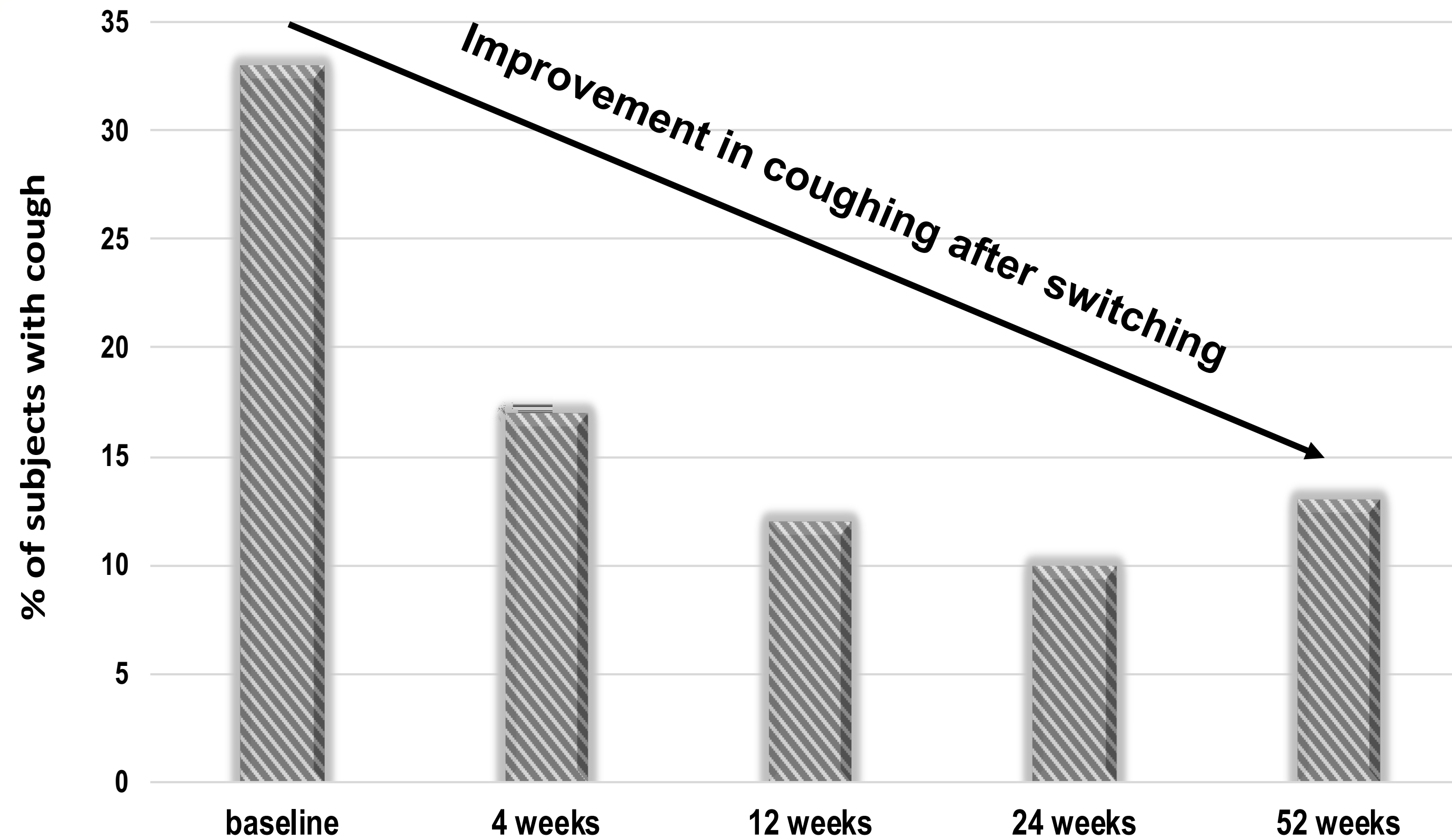
Exhaled Breath

- Nitric oxide (FeNO)
- Carbon monoxide (eCO)
- EB Condensate analysis

Imaging

- Angio OCT
- High-Resolution CT
- Hyperpolarized MRI

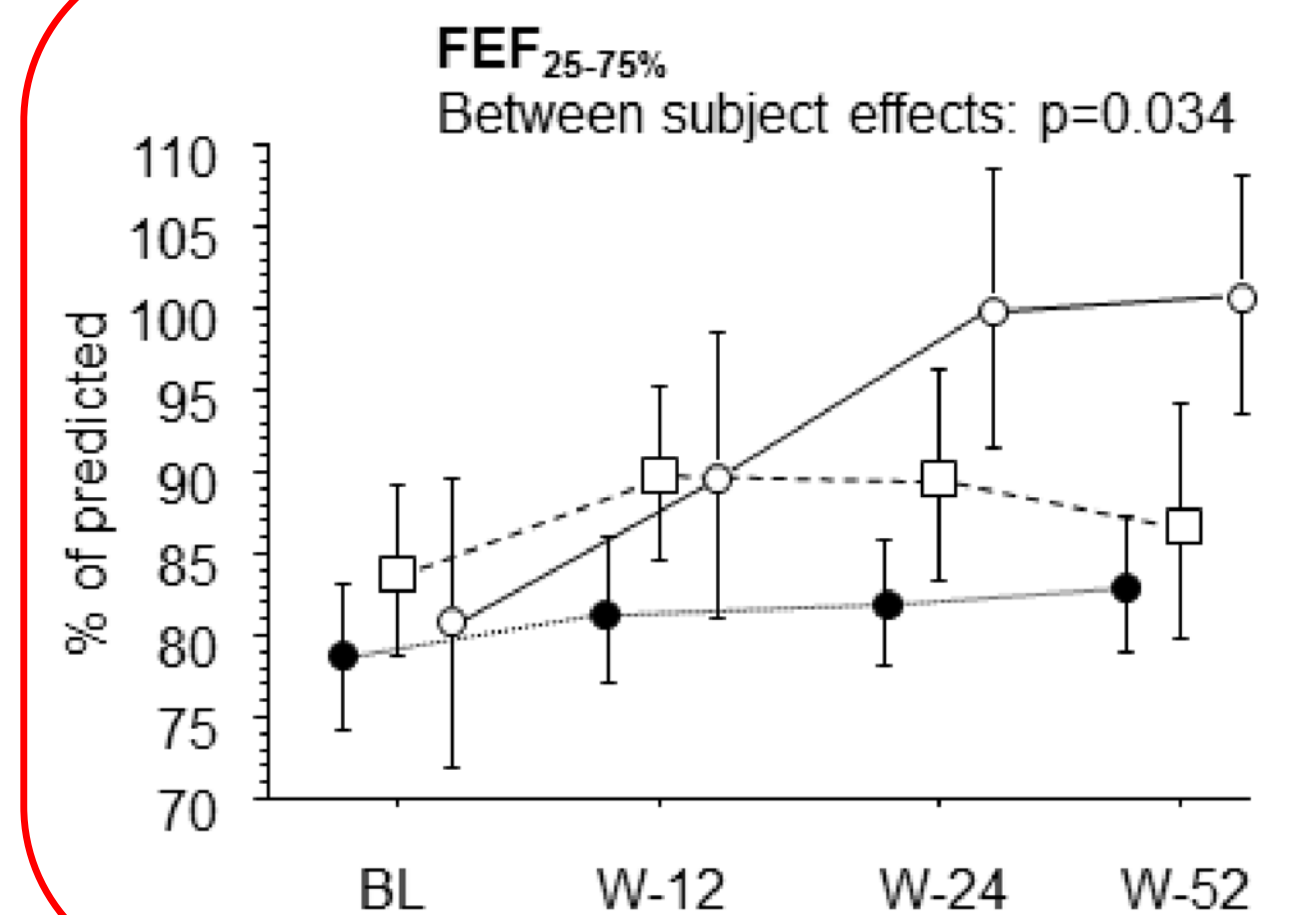
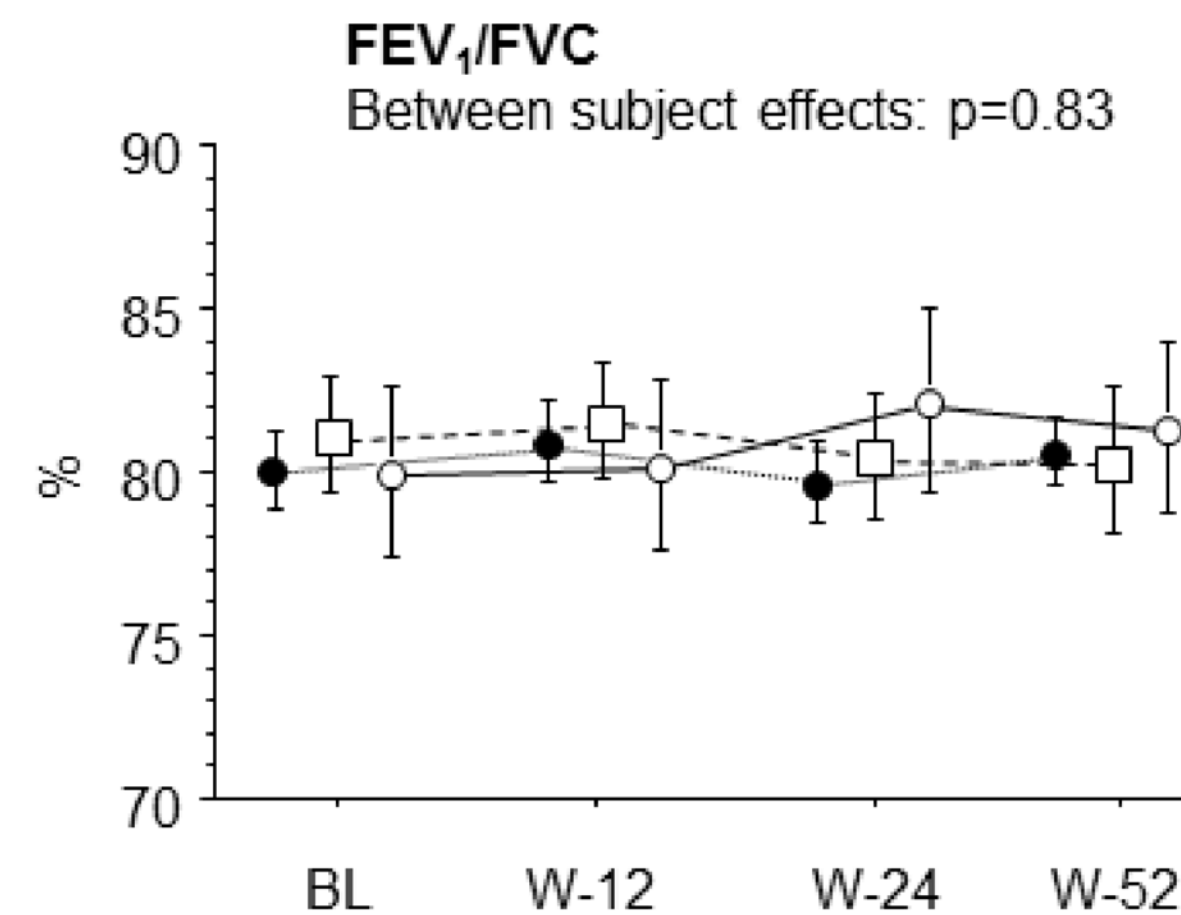
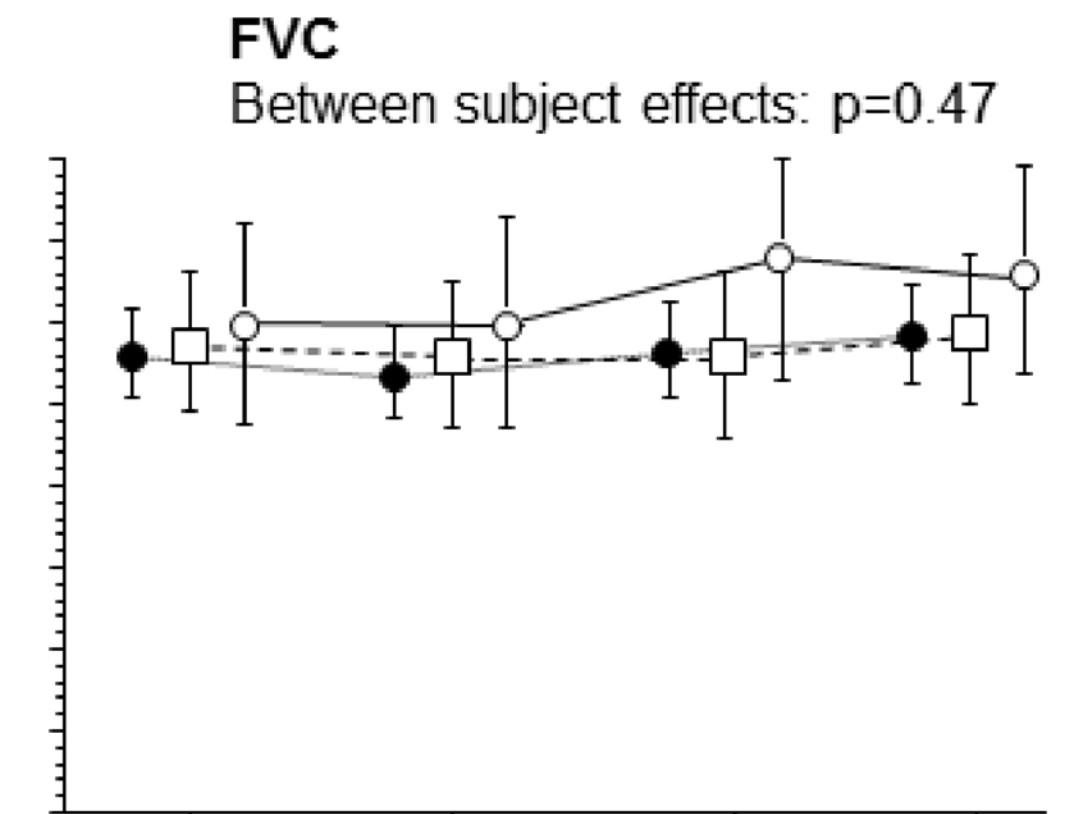
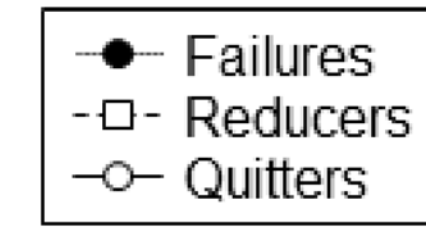
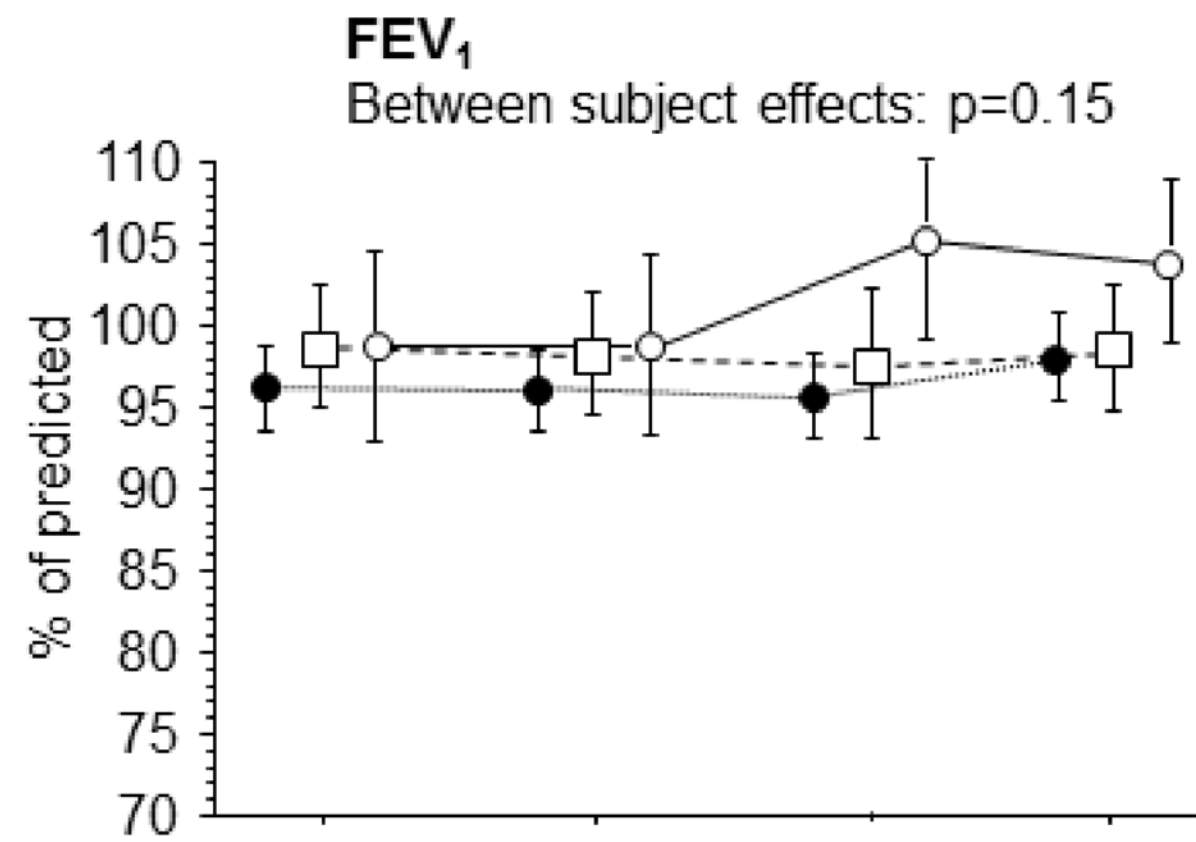
Reduction in cough by regular EC users who abstained from tobacco smoking after switching



Functional Evaluations



Spirometry

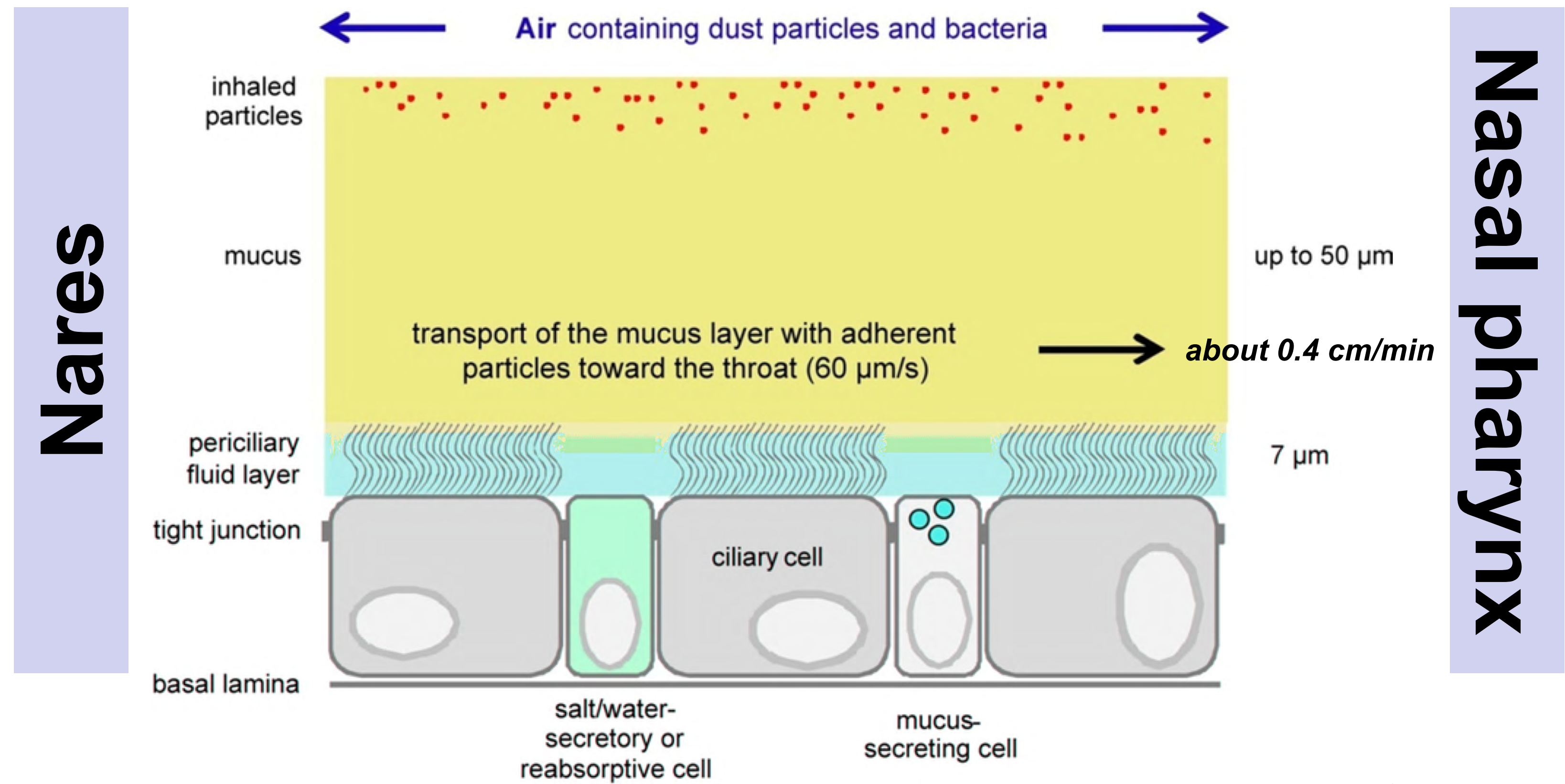


Functional Evaluations

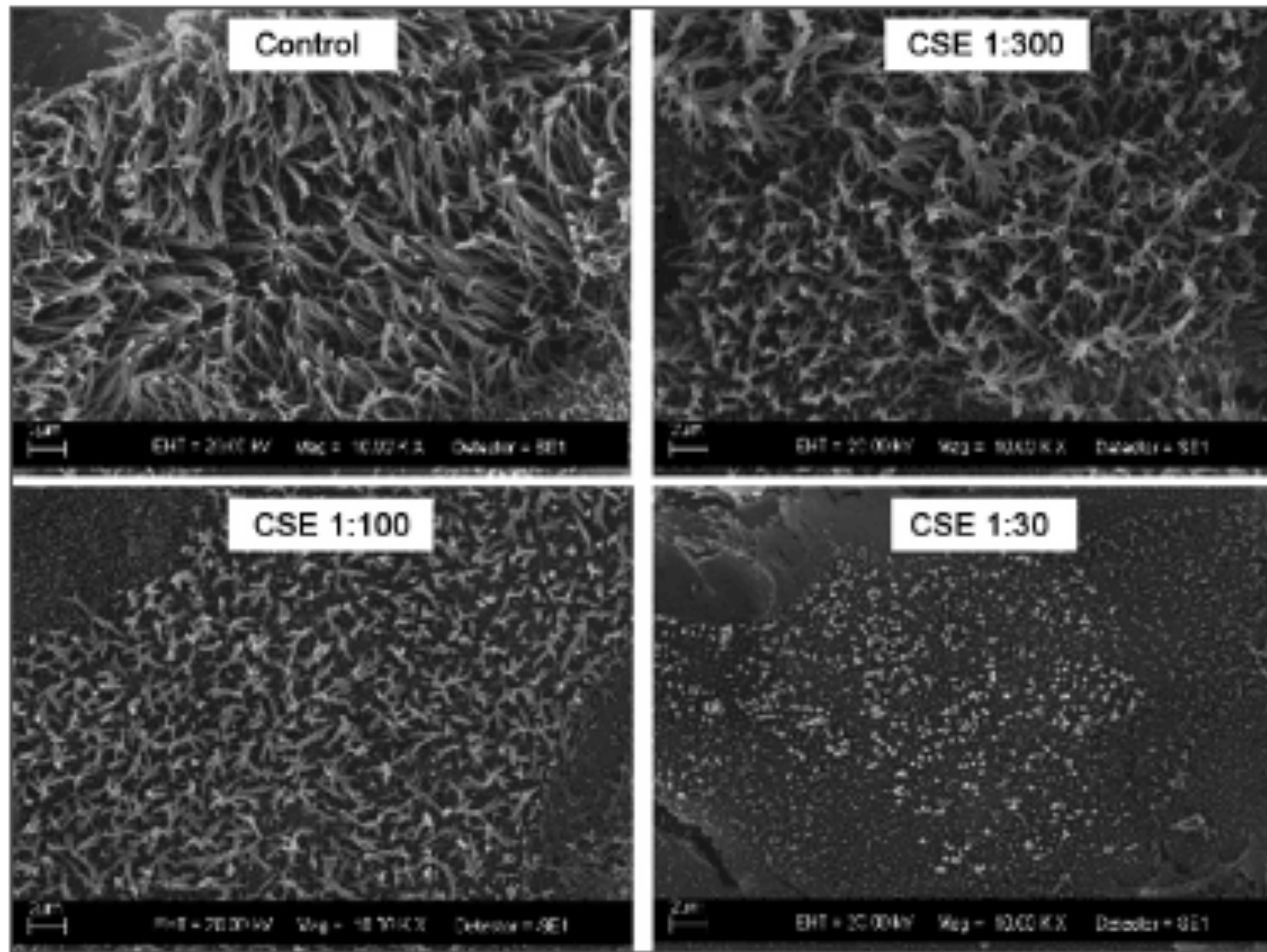
Mucociliary Clearance (MCC)



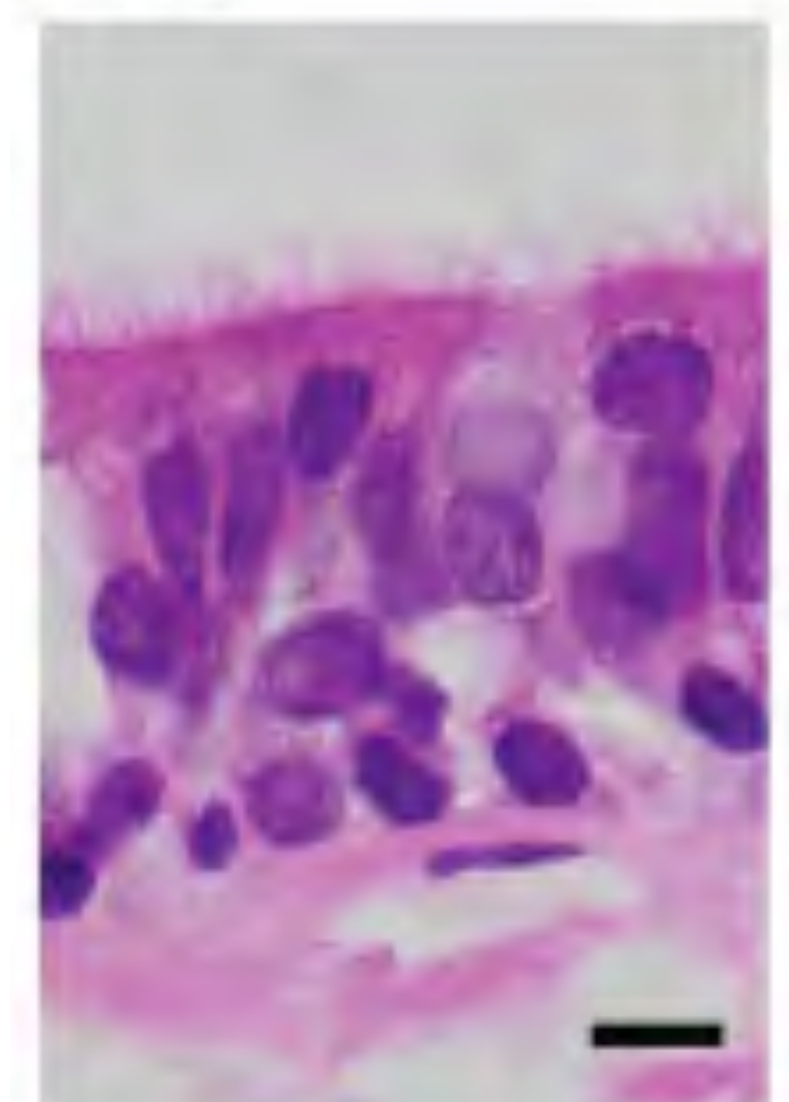
Saccharin particle is placed in the medial surface of the inferior nasal turbinate.



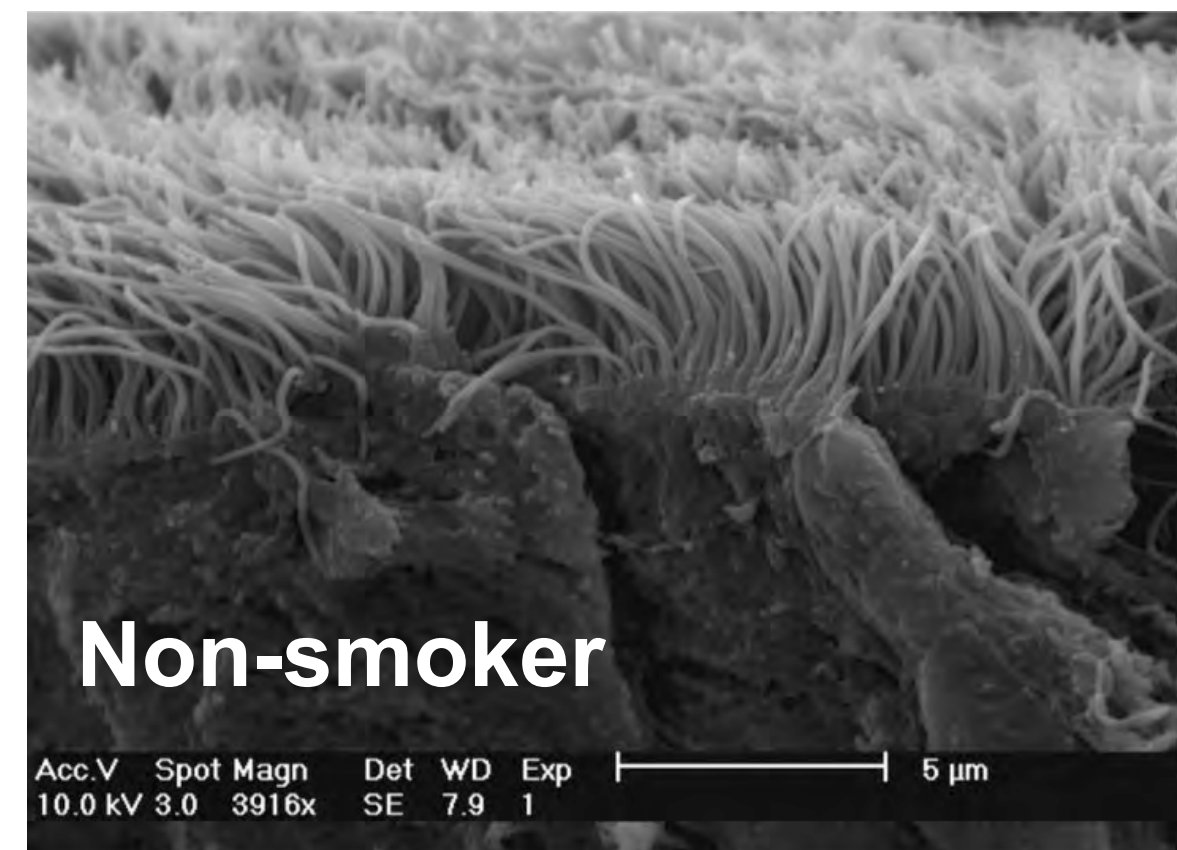
Harm caused by cigarette smoke on respiratory cilia



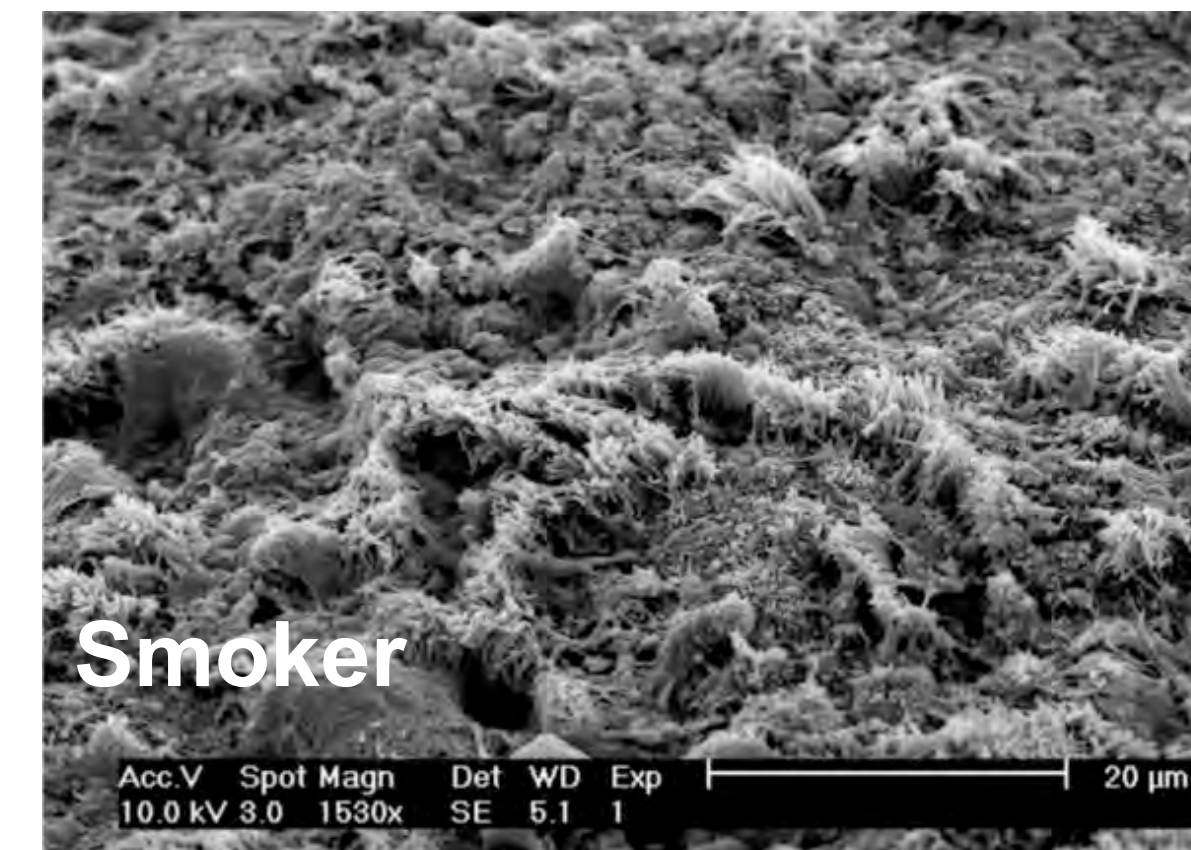
Non-smoker



Smoker



Non-smoker



Smoker

Figure 2. Scanning electron microscopy photographs showing the dose-dependent effect of cigarette smoke on cilia size after exposure to decreasing dilutions of the Cigarette Smoke Extract (CSE).

Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance

R. Polosa , R. Emma, F. Cibella, M. Caruso, G. Conte, F. Benfatto, S. Ferlito, A. Gulino, M. Malerba and P. Caponnetto

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Saccharin test transit times (min)



Upper Limit of Normality value = 11 min

Switching Can Restore Lung Defence

Imaging Evaluations

Imaging parameters via HRCT

1) density threshold measures

- lung attenuation area (LAA <950 HU, Perc-15 on TLC series)
- percent air trapping (all <860 HU on RV series);

2) texture feature measures

- percentage of ground glass (QGG, pulmonary fibrosis; QLF, normal lung ; QN as percentage pixels, and ml);

3) airway measurement

- median airway wall thickness (WT, square root of wall area - SRWA, and diameter and Pi10)



Imaging Evaluations



- Non-invasive imaging technique
- Quantitative parameters of retinal microcirculation
- Superficial and deep capillary plexus

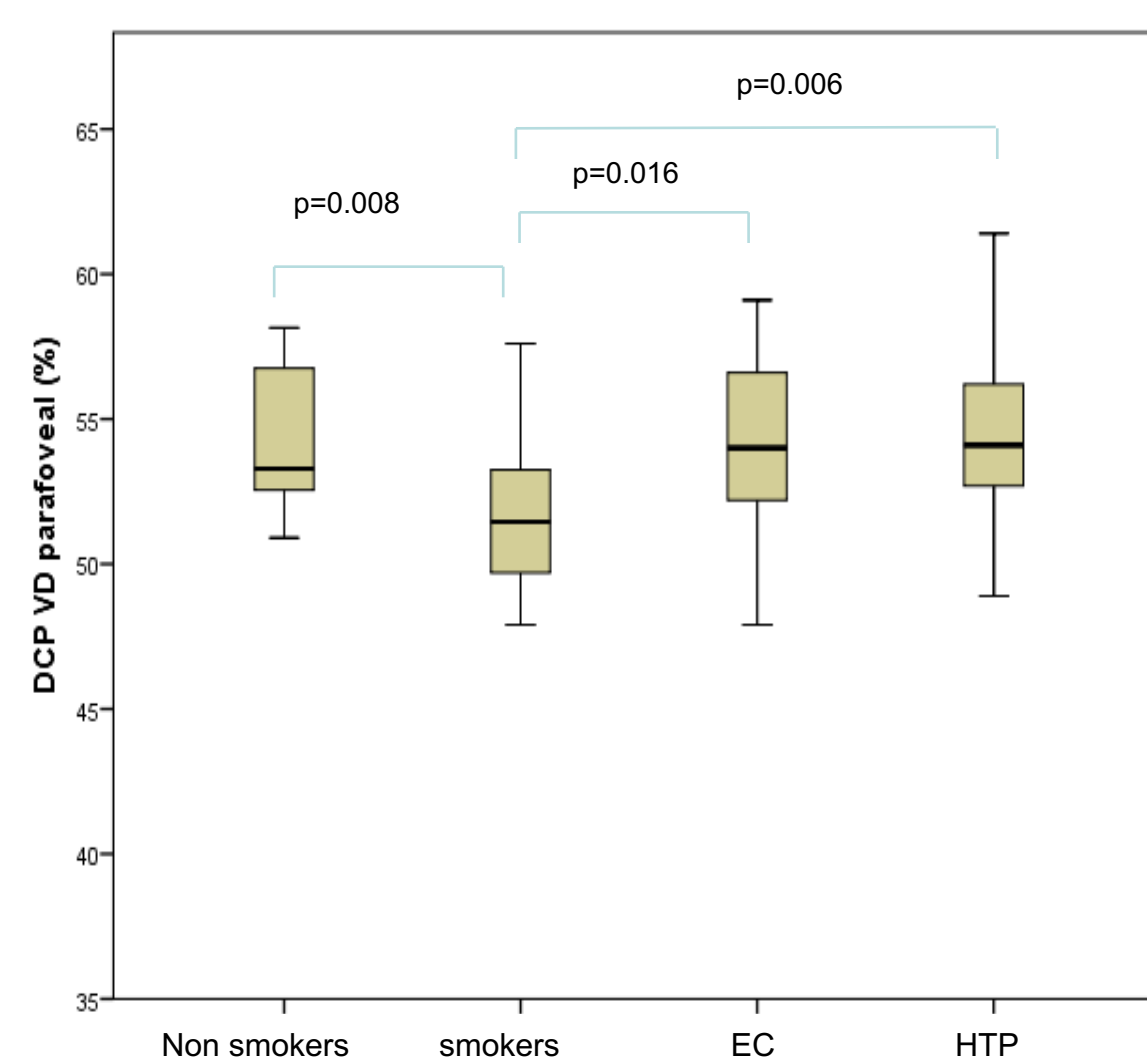
Imaging parameters via optical coherence tomography (OCT)

- 1) Retinal thickness
- 2) Superficial retinal vessel density

- Whole
- Fovea
- ParaFovea;

3) Deep retinal vessel density

- Whole
- Fovea
- ParaFovea;





Key Issues

- Existing study endpoints are not sensitive enough and not clinically significant
- Evidence for an health-focused MRTP claim may require:
 - *Novel, clinically relevant health effect indicators*
 - *A combination of existing and novel health effect indicators*
- Discovery science programs to inform regulatory science of novel tobacco and nicotine products
- The long-term health impact requires prospective studies of users with no previous hx of exposure to tobacco smoke