

## **Online supplement 5.**

### **Priorities for future research in exhaled VOCs**

#### **Important areas for future research are listed below:**

1. Compose standard, complex gas mixtures as reference sample to test/calibrate equipment including any pre-processing steps (*e.g.* sorbent tubes).
2. Establish which sampling technique gives best discrimination for respiratory diseases and guarantees simplicity, reproducibility and adequate hygiene in a multi-centre setting.
3. Explore integration of exhaled breath collection with existing pulmonary function instruments [1]. Carry out independent proof of concept study to assess if commercially available devices are capable to discriminate between relevant patient groups.
4. Develop a standard, reproducible procedure for exhaled breath collection on a transportable medium allowing pre-concentration and multi-centre studies for which examples are available [2].
5. Test the validity of using mixed versus alveolar gas samples for particular diseases and disease outcomes.
6. Develop a new sensor technology that allows for semi-selective recognition of target VOCs.
7. Develop innovative instruments for VOC analysis merging existing transducer technologies and chemical interactive materials.
8. Establish the most appropriate processing and classification methods for complex exhaled breath signals [3].
9. Facilitate statistical analysis by setting up VOC and e-Nose datasets in a public database that can be accessed and analysed by several groups and diverse statistical procedures. Provide a standard dataset that shows robust analysis results. Provide recommendations for proper analysis (potentially by validated R procedures).
10. Establish an open access VOCs and VOC patterns repository for clinical usage.
11. Perform chemical identification of clinically relevant compounds.

### **2.2. Priorities for clinical research on exhaled VOCs**

1. Examine within-patient alterations in exhaled VOCs during changing disease states and/or responses to therapy.
2. Perform multi-centre studies to externally validate algorithms for discriminating VOC patterns between diseases and patient groups.
3. Evaluate the added predictive value of VOC analysis to commonly available clinical, radiological and biochemical information.
4. Link exhaled VOC patterns and individual components to biological pathways.
5. Focus on disease prediction, phenotyping, monitoring and disease exacerbations.
6. Examine performance of exhaled breath analysis in routine medical care and real-world populations including variability in age, gender, ethnicity, smoking, co-morbidities, levels of therapy and geographical area.
7. Design collaborative studies in order to ensure: adequate sample numbers, clinically relevant control groups (as opposed to healthy controls only), and ensure external validation.

## References

1. de Vries R, Brinkman P, van der Schee MP, Fens N, Dijkers E, Bootsma SK, de Jongh FH, Sterk PJ. Integration of electronic nose technology with spirometry: validation of a new approach for exhaled breath analysis. *J Breath Res* 2015; 9(4): 046001.
2. Pennazza G, Santonico M, Incalzi RA, Scarlata S, Chiurco D, Vernile C, D'Amico A. Measure chain for exhaled breath collection and analysis: A novel approach suitable for frail respiratory patients. *Sensors and Actuators B: Chemical* 2014; 204(0): 578-587.
3. Gromski PS, Correa E, Vaughan AA, Wedge DC, Turner ML, Goodacre R. A comparison of different chemometrics approaches for the robust classification of electronic nose data. *Anal Bioanal Chem* 2014; 406(29): 7581-90.