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Asthma Breathomics and Biomedium Consideration

To the Editor:

We read with great interest the recent review article by Kelly et al[1] in the February 2017 issue of *CHEST*; however, we note that there are some points that were perhaps not fully elucidated regarding breath sampling. Four of the studies considered as analyses of exhaled breath condensate (EBC) were in fact studies of exhaled breath (EB); we believe that there are fundamental differences here because the former is a fluid medium, whereas the latter involves direct sampling of volatile organic compounds (VOCs) in the breath. Although VOC precursors may be found within EBC, and examination of the EBC–VOC interface is likely to be of importance in understanding VOC-generating metabolic pathways,[2] the two mediums involve quite different methodologies.

The review provides a useful synthesis of asthma metabolomics across different biomediums; however, some relevant publications seem to have been omitted. Systematic searches of asthma breathomics across multiple databases can be found in reviews[3] and commentaries.[4] These have identified an additional 11 studies in EB research alone. The findings of these missing studies largely support the conclusions of Kelly et al[1]: that metabolomic profiles have a high discriminative ability for asthma identification, but there exists here an opportunity to identify further compounds that have been replicated in more than one study.

Kelly et al[1] rightly highlight the lack of standardization in the field, but guidelines have recently been published for both EB and EBC.[5] It is likely that these, coupled with the availability of "off the shelf" breath sampling devices and a drive toward standardization of data processing and statistical analysis, will lead toward increased inter-study comparability and the validation of results in independent cohorts, which are key steps toward the clinical application of breathomics.

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Response

To the Editor:

We thank Peel et al for their comments. We acknowledge that breathomics was underrepresented in our review[1] and that we failed to appropriately distinguish exhaled breath (EB) and exhaled breath condensate (EBC). We agree that breath metabolomics represents an exciting facet of asthma research that may have substantial for potential for clinical translation. We also wish to make the following points.

Breathomics has been defined as the "metabolomics of breath"; however, it is interchangeably used to include eNOSE studies,[2] which are not, in our opinion, inherently "metabolomic" in nature. Fewer than one-half the breath-based studies included in our review used the term "breathomics," and the lack of consistency even of terminology in metabolomics complicates the synthesis and interpretation of the literature. Further, although, as Peel et al note, some published standards for breath-based studies exist, they have not been universally adopted.[3] EBC and EB are still plagued by issues inherent to all metabolomics studies, including incomplete coverage, measures of relative abundance, highly dimensional noisy data sets and confounding, as well as breath-specific challenges such as the absence of a valid dilution factor for

EBC.[4] Regardless, both EBC and EB have notable advantages over other biosamples, primarily their noninvasive collection and their proximal relationship to the lung and respiratory tract. Accordingly, impressive results have been reported from breath-based studies.[2,4] Replication of significant findings is a key issue for metabolomics. The relevant studies noted by Peel et al that were not included in our original review[1] strengthen our conclusions and demonstrate replication for additional metabolites noted in our review, including decane, 4-isopropenyl-1-methylcyclohexene, 1-isopropyl-3-methylbenzene, pentane, and methylated alkanes,[2] providing further evidence for their role in asthma.

We welcome the news that international collaborations are working to provide guidelines for standardized methodology to maximize across-study comparability.[3] We also second the call by van der Schee et al[5] for the development of a "breath cloud" to aid the development of translatable biomarkers. Such initiatives are vital to move the field forward, and we hope that with the collaboration of the whole asthma metabolomics community, including those with expertise in breath, we will soon see the first metabolic biomarkers of asthma in the clinic.

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Weekday and Survival After Pulmonary Resections for Lung Cancer

A Swedish Nationwide Cohort Study

To the Editor:

Political concerns have been raised regarding differences in quality of care influencing survival and of a possible relation to weekday of hospital admission or treatment.[1] A decreased short- and long-term survival related to weekday of surgery, in a variety of surgical disciplines, has been reported,[2-4] but the results are conflicting.[5] Current evidence is not sufficient to conclude whether weekday of surgery influences survival following surgery for lung cancer in Sweden. We performed a nationwide observational population-based cohort study investigating long-term survival following lung cancer surgery. The aim was to analyze the association between weekday of surgery and survival following pulmonary resections for lung cancer.

The study was approved by the Human Research Ethics Committee, Stockholm, Sweden, and the need for informed consent was waived. The Swedish national quality register for general thoracic surgery (ThoR, http://www.ucr.uu.se/thor) was used to identify the study population. All patients registered in ThoR who underwent pulmonary resections for lung cancer between January 1, 2009, and December 31, 2015, were included. The ThoR register was started in 2008 and a complete coverage of all eight thoracic surgery departments in Sweden was achieved in 2013. From 2009 to 2011, approximately 50% of all patients who underwent thoracic surgery in Sweden were included, and during 2011 and 2012, seven of eight hospitals reported to the register. The primary outcome measure was all-cause mortality and vital status was determined on April 15, 2017, by using the Swedish population register. We fit crude and adjusted Cox regression models to estimate the association between weekday of surgery and survival.

A total of 4,528 patients were included, and 1,137 (25%), 1,018 (22%), 1,001 (22%), 889 (20%), and 483 (11%) patients underwent surgery Monday through Friday, respectively. Baseline characteristics were similar across weekdays (Table 1). There were no significant