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## **Asthma in one breath: metabolic signatures for allergic asthma in children by real-time breath analysis**

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We hypothesized that the breath of children with allergic asthma contains a unique signature of disease specific metabolites. Using secondary electrospray ionization high-resolution mass spectrometry (SESI-HRMS), we aimed to identify relevant VOCs to assess underlying interconnections between biomarkers belonging to common metabolic pathways in the pathophysiology of asthma.

Breath analysis was performed on an TripleTOF 5600+ HRMS ( $m/z$  range 50 - 500, mass accuracy < 2 ppm) coupled to a SUPER SESI ion source. A combination of data extraction and machine learning was used to isolate discriminative  $m/z$ -features and assess the predictive power of breath profiles. Putative compound identification was performed based on MS/MS spectra recorded from breath, screening for biological relations and subgrouping into metabolic pathways and chemical families.

We acquired breath samples from 104 children aged 11.02 ( $\pm$  3.59) yrs, 48 with allergic asthma, 56 healthy controls resulting in 2315  $m/z$ -features in total, of which 375 were significantly different between the two groups. Supervised machine learning resulted in an area under the curve (AUC) of 0.86 (95% CI: 0.76 - 0.95) for classifying asthmatics vs. healthy. The following pathways and chemical families were elevated in asthmatic children: lysine degradation, tyrosine metabolism, 2-oxocarboxylic acid metabolism, fatty acid metabolites and monosaccharides.

We are the first to report such a richness of significant  $m/z$ -features in exhaled breath of children, a large amount of identified compounds and almost entire metabolic pathways that might be directly connected to underlying pathological mechanisms of allergic asthma.

#equal contr.