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| **Predicting future exacerbation in uncontrolled asthma: A discovery/validation approach using large-scale clinical proteomics** |
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| **Introduction/Aim:**  Severe exacerbation contribute significantly to the burden of asthma. Prior exacerbations requiring systemic steroids in the previous 12 months are traditionally the best tool for predicting future exacerbations.  Building upon our discovery analysis, we aimed to validate a predictive sputum signature for future exacerbations, using clinical samples and data obtained from the AMAZES study (Lancet, 2017) which established that macrolides reduce exacerbations.  **Methods:**  In order to validate our predictive signature associated with future exacerbations, 123 samples from the control (placebo control) arm of the AMAZES study was analysed using a robust targeted mass spectrometry method. Samples were selected and stratified based on asthma exacerbation during clinical follow up (48 weeks). Protein intensities of the top 20 most influential proteins from our discovery analysis were selected for validation and quantification. Proteins found to be linked to future exacerbations were analysed using our previously establish multivariate model using sparse partial least squares data analysis using MixOmics package.  **Results:**  Of the top 20 most influential proteins identified in our discovery exacerbation signatures, 9 proteins were found to be linked to future exacerbation risk. Our final model could predict future exacerbation with an area under the receiver-operating curve of 0.77 with an error rate of 0.40. Pathway analysis revealed major theme associated with exacerbations including inflammation, recruitment, and proliferation of immune cells.  **Conclusion:**  This study has identified for the first time a sputum proteomic signature and pathways associated with future exacerbations, which will facilitate the discovery of new biomarkers and novel therapeutic targets in uncontrolled persistent asthma.  **Grant Support:**  NHMRC project APP1144941 |