Exploring heterogeneity in Pulmonary Hypertension

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Background: Pulmonary Hypertension (PH) is defined by an elevated mean pulmonary artery pressure (mPAP) greater than 20 mmHg. PH can develop rarely in isolation, more commonly in association with other cardiovascular or respiratory diseases, or most commonly as a secondary comorbidity to primary cardiovascular and respiratory diseases. In all instances PH imparts a poor prognosis regardless of cause, and is commonly underdiagnosed, creating significant healthcare burden. Estimates suggest that 1% of the global population have increased mPAP making PH and a silent killer with treatments limited to specific classification groups. The clinical classification of PH used to assign treatment comprises 5 groups based on disease aetiology and haemodynamic measurements obtained by right heart catheterisation; namely, Group 1 - Pulmonary Arterial Hypertension (PAH); Group 2 - PH due to left heart disease (e.g. heart failure); Group 3 - PH due to lung disease and/or hypoxia (e.g. COPD); Group 4 - PH due to pulmonary artery obstruction; Group 5 - PH with unclear and/or multifactorial mechanisms. Groups 1, 4 and 5 encompass rare diseases with 5,000 people in the UK undergoing active drug treatment. However, many more people live with undiagnosed, or untreated PH, most frequently associated with left heart failure (Group 2) and chronic lung disease (Group 3).

The problem: Evidence highlights that 40% PH of patients present with clinical features that overlap two or more classifications. PH presents with common and non-specific symptoms such as breathlessness and fatigue which often lead to a delay in seeking medical advice. This can be further compounded by the presence of cardiovascular and/or respiratory comorbidities and frequent delays between initial symptom onset and diagnosis (~3 years) which leads to a heterogeneous population of patients, both in terms of clinical features and severity of disease. Even within individual classification groups there is significant heterogeneity, with a total of 32 sub-groups spread across the 5 main classifications. Within the most widely studied classification group, PAH there are now multiple drugs targeting 4 main pathways but there are many more diverse molecular mechanisms described within the literature. **The solution:** We have recently taken an unsupervised clustering approach whole blood transcriptomics and identified 5 clusters within the idiopathic subgroup of PAH. Identifying clusters, and their association with clinical features will be key to stratifying current, and identifying new treatments of pulmonary hypertension is it broadest most heterogenous forms. The presentation will provide an overview of areas of heterogeneity and discuss approaches to develop better tools to cluster and stratify patient using various datasets.