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Editorial

Bringing Systems Medicine to Paediatrics

"On ne voit bien qu'avec le coeur, l'essentiel est invisible pour les yeux", wrote Antoine de Saint-Exupéry in *Le Petit Prince*. It is with your heart that you feel essentials that are invisible to your eyes. Eyes of reductionists focus on preconceived matters of consequence. Sir William Osler said, "The good physician treats the disease, the great physician treats the patient who has the disease." Diagnosis precedes treatment. Are we then just diagnosing disease, or should we be trying to understand and diagnose perturbation of the patient's health milieu that results in the disease?

In this issue of the Journal, two articles explored the value of serum biomarkers in diagnosing and predicting occurrence of childhood illnesses. Feng et al evaluated the value of procalcitonin and C-reactive protein as predictors of appendiceal perforation in children with acute appendicitis.[1] They found that procalcitonin has the highest sensitivity and specificity in predicting occurrence of this complication in 201 children with a mean age of 7.6 years, as compared with the use of C-reactive protein. In another study, Dorum et al evaluated the diagnostic value of serum amyloid A in early-onset neonatal sepsis in preterm infants born 24 to 36 weeks of gestation.[2] They found that serum levels of amyloid A, as compared to C-reactive protein and procalcitonin levels on admission, at 24 hours, and at 48 hours, have the greatest area under the curve by receiving operating curve analysis for diagnosing early-onset neonatal sepsis. The aforementioned studies explored the use of circulating biomarkers known to be associated with the body inflammatory response for diagnostic purposes. Blood delivers oxygen and nutrient to different organs, removes waste from body tissues, and carries in the circulation information on how the body reacts to different diseased conditions. Hence, circulating biomarkers of inflammation, albeit non-specific for the underlying disease condition or unrevealing of the underlying pathogenesis, have been commonly used to aid the diagnosis of infective and inflammatory conditions in children.

Novel approaches that utilise cutting edge technologies are increasingly used to identify new biomarkers, which may be involved in the pathogenesis, in paediatric conditions. As an example, recent studies in patients with Kawasaki disease aimed to analyse the serum proteome to identify candidate protein markers that may help in diagnosing and understanding the pathogenesis of Kawasaki disease. Kimura et al used mass spectrometry-based proteomics analysis and identified differential expression of about 1800 proteins during the acute and recovery phases of the illness.[3] Of these, three proteins were found to be higher during the acute phase of the illness and may facilitate diagnosis of Kawasaki disease. Lech et al performed more extensive molecular profiling with mass spectrometry-based shotgun proteomics, transcriptomics, and glycomics in paediatric and adult patients with Kawasaki disease.[4] These investigators found that complex patterns of biomarkers of inflammation and cell trafficking can persist long after the acute phase of Kawasaki disease. These studies represent endeavours of the paediatric community to study disease

conditions using the multi-omics approach to understand perturbations and to unveil more specific and novel diagnostic markers in childhood conditions from the perspective of the whole body system.

A fundamental concept of systems medicine is to view the human body as a network of networks.[5-7] Each level of biological complexity, from genome to phenome, from cells to organ, and from molecules to individuals, can be conceptualised and modeled as networks with specific components and interactions among these various networks.[5] This holistic perspective of a network of networks is in sharp contrast with the reductionistic view of a handful of pathways to explain causal pathophysiological relationships between the aetiologic factors and disease occurrence. From the perspective of systems medicine, it is perhaps not difficult to understand the disagreement among different studies of usefulness of biomarkers in diagnosing specific conditions and the difficulties of translating the biomarker assay for clinical use. In essence, the non-linear physiological responses to internal health milieu and external stimuli renders interpretation of the biological and pathophysiological variations of circulating biomarkers difficult. It is intuitive, therefore, to design studies that take into account of the complexity and variability of human physiology, which would entail the collection and analyses of multi-dimensional datasets. The pioneering wellness study of 108 individuals using personal, dense, dynamic data (pD3) clouds has clearly demonstrated the feasibility of building a dataset that can be mined for novel biological and medical discoveries.[8] In this project, personal data including whole genome sequences, proteomes, metabolomes, gut microbiomes, and clinical laboratory results were collected over a nine-month period. Importantly, integration of the data generated 3470 statistically significant cross-sectional correlations. The correlation network had revealed communities of related analytes associated with physiology and disease and that the connectivity further enabled identification of known and candidate biomarkers.

Generation of pD3 clouds of children in health and disease is yet to be materialised. Nonetheless, large amounts of paediatric data that provide information on prenatal well-being, postnatal growth, neurodevelopmental milestones, childhood illnesses, hospitalisations, use of medications, vaccination, and lifestyle-related information are continuously collected, albeit residing in different database. How to harness the power of these health information, how to systemically collect the multi-omics dataset, and how to generate bioinformatics and big data platforms for their integrated analysis are challenges that need to be solved to bring system medicines to paediatrics.

YF Cheung
Chief Editor

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