13 (28%) patients had CKD stage 3. 6/13 had low predicted risk of progression at 5 years of whom 4/6 progressed unexpectedly. 1/13 was identified as having high risk at 5 years and that 1 patient progressed to CKD5D/T.

6/18 CKD 3/4 patients with predicted low risk progressed to CKD5D/T unexpectedly. 1/6 had emergency abdominal surgery, 1/6 patient had unexplained rapid progression and 4/6 had acute upper gastro-intestinal haemorrhage causing terminal decline of kidney function.

Conclusions: The number of patients analysed was small. The 8-variable equation accurately predicted high risk of progression to CKD5D/T in 7/9 CKD3/4 patients.

Conversely, 6/18 patients with predicted low risk progressed to CKD5D/T. Acute medical events including upper gastro-intestinal bleed accounted for most instances of unexpected progression.

SAT-194

PLASMA PEPTIDOMICS BASED MULTIVARIABLE MODEL FOR THE CLASSIFICATION OF HYPERTENSIVE FROM NORMOTENSIVE SUBJECTS IN CKD

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Introduction: Hypertension is a major risk factor for cardiovascular disease and is also a risk factor for chronic renal failure. Despite of advancements in lowering blood pressure, the best approach to lower it, remains controversial due to the lack of information on its development. We therefore, performed plasma proteomics to identify the markers discriminating hypertensive from normotensives.

Methods: Plasma samples from hypertensive (n=118) and normotensive subjects (n=85) from the "InGenious Hypercare" cohort were used for the study. We performed liquid chromatography online coupled to electrospray ionization quadrupole ion trap mass spectrometry for analysis of the plasma samples. Hypertension specific plasma peptides were identified and a model was developed using least absolute shrinkage and selection operator logistic regression. The underlying peptides were identified and sequenced offline using matrix assisted laser desorption ionization mass spectrometry. Further, to get an insight in to the mechanisms, pathway analysis was performed using KEGG and GO databases.

Results: By comparison of plasma samples, 27 biomarkers were identified discriminating hypertensives from normotensives. 70% of the features selected were found to occur less likely in hypertensive patients. A cross-validated predictor model was developed with the overall R square of 0.434 and the area under the ROC curve was 0.891 with 95% confidence interval 0.8482 to 0.9349, $P<0.0001$. The mean value of the cross-validated predictor score of normotensive and hypertensive patients was found to be -2.007 $\pm$ 0.3568 and 3.383 $\pm$ 0.2643, respectively. Phosphtidylinositol 3 kinase regulatory, humanin, anoctamin 10, NIK related protein kinase, Mannose-6- phospho isomerase, tryptophan, erythrocyte membrane glycopeptide, transcription factor Dp-2, pleckstrin homology domain-containing family O member 1, cardiac phospholamban, osteocalcin or sarcolipin, ras-related protein Rab-13, protein prune homolog, nexilin and palladin were the identified peptides. The pathway analysis revealed that these proteins had mostly cardiac related functions.

Conclusions: Plasma proteomics model was able to predict the hypertensive-normotensive status based on 27 molecular features. After validation in other cohorts for reproducibility, the identified markers may be useful to clarify the causes of hypertension and to predict the development of hypertension and hence of cardiovascular events.

SAT-195

DIAGNOSTIC UTILITY OF WHOLE-EXOME SEQUENCING IN A CHRONIC KIDNEY DISEASE COHORT

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Introduction: Genomic technologies enable the rapid and cost-effective sequencing of DNA and have demonstrated a definitive diagnosis in several patient groups. The clinical utility of whole exome sequencing (WES) in a kidney disease cohort is not yet well established. We describe the patient characteristics and diagnostic yield of a cohort of 200 patients with suspected genetic kidney disease referred for WES via a multidisciplinary renal genetics clinic.

Methods: 200 sequential patients were recruited into a prospective observational cohort study through five tertiary academic centres in Victoria, Australia. Patients were referred by their treating nephrologist to a dedicated renal genetic service funded by the Melbourne Genomics Health Alliance. Following review by a multidisciplinary team, consisting of a nephrologist, clinical geneticist and genetic counsellor, patients were recruited for genomic sequencing, with analysis for a pre-determined list of genes of interest. We measured the diagnostic yield and its effect on short term clinical management.

Results: Singleton WES was performed on 123 adult patients and 83 paediatric patients. Majority were female (118) and median age was 27 years (range 0-73 years). 100 of these patients were isolated cases (77 had a known positive family history). From 104 exome results available to date (38 paediatric and 66 adults), 43 patients received a positive molecular diagnosis (41%) and of these 22 (51%) resulted in a change from the original clinical diagnosis. The diagnostic yield was greater in the paediatric cohort (53%) compared to the adult cohort (35%). The effects of genomic testing on clinical management is currently being analysed.

Conclusions: Singleton WES resulted in a substantial number of positive diagnoses in both adult and paediatric patients. The ongoing analysis of this cohort will allow delineation of the sensitivity of exome sequencing to current diagnostic methods, enable health economic analysis of testing and facilitate identification of the clinical predictors of a positive diagnosis. To our knowledge, this is the largest prospective kidney disease cohort to undergo whole exome sequencing with integrated utility analysis to date.

SAT-196

HOW TO ESTIMATE GLOMERULAR FILTRATION RATE IN SUB-SAHARAN AFRICA: DESIGN AND METHODS OF THE AFRICAN RESEARCH ON KIDNEY DISEASES (ARK) STUDY

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Introduction: Chronic kidney disease (CKD) is a substantial cause of morbidity and mortality worldwide with disproportionate effects in sub-Saharan Africa (SSA). The optimal methods to accurately estimate glomerular filtration rate (eGFR) and therefore facilitate identification of CKD among African populations are uncertain. We plan to measure iohexol excretion and correlate measured GFR with existing equations to determine the optimal methods to estimate GFR and determine the prevalence of CKD in Malawi, South Africa and Uganda

Methods: The African Research on Kidney Disease (ARK) study is a three country study embedded within existing cohorts. We seek to enrol 3,000 adults >18 years stratified by eGFR using baseline serum creatinine. Study procedures include questionnaires on socio-demographics and potential risk factors for kidney disease, anthropometry, body composition, blood pressure, blood chemistry and urine microscopy and albuminuria. All participants will have a measured GFR (mGFR) by plasma clearance of iohexol at 120, 180 and 240 minutes. Blood and urine samples will be bio-banked.

Results: The eGFR determined by established equations will be compared with mGFR to establish the most accurate method to estimate GFR in this population. We will present the population prevalence of CKD, both overall and stratified for risk factors of interest, for the three countries. In addition, our results will provide detailed information about risk factors associated with CKD in these populations.
Conclusions: The ARK study draws participants from three countries with harmonised protocols which will increase the applicability of the findings across the region and permit identification of population differences. The study is embedded within established cohorts that have background information and serial measures that can be used to characterize incidence and progression of CKD. This study will overcome the limitations of previous research including the use of single creatinine measures, small numbers or non-population-based sampling strategies, and address the lack of data on proteinuria/albuminuria as recommended by Kidney Disease: Improving Global Outcomes (KDIGO). The ARK collaboration provides a strong platform for kidney disease research, within the context of infectious and non-communicable diseases in SSA. Through harmonized study procedures and sample collection, and pooling of data sets, we hope our results will contribute to strengthening health systems and informing public health policy for the screening, prevention and treatment of CKD in the region. We welcome additional partners from across the continent.

SAT-197

ESTABLISHING A HUMAN KIDNEY CULTURE MODEL TO TEST PLANT-DERIVED CHRONIC KIDNEY DISEASE THERAPIES

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Introduction: Chronic kidney disease (CKD) is increasing in incidence globally, and current CKD therapies (angiotensin converting enzyme inhibitors/ACEi or angiotensin receptor blockers/ARBs) are only moderately effective, highlighting the need to accelerate research into new pharmacological approaches. One of the known causes of CKD is oxidative stress. This project aimed to develop a reliable human pre-clinical model of oxidative-stress induced CKD to examine the benefits of adjunct or complementary therapies for CKD treatment.
Methods: Primary human kidney proximal tubular epithelial cells (PTEC) were isolated from healthy kidney from cancer nephrectomies from consenting Royal Brisbane and Women's Hospital patients. To develop a CKD oxidative stress model, PTEC were cultured alone or under low-dose (0.4mM hydrogen peroxide; H_2O_2) or high-dose (0.8mM H_2O_2) oxidizing conditions over 24h, 48h and 72h. The ACEi Enalapril was used at 50 or 500 μM with and without H_2O_2 in some experiments. PTEC were assessed for morphology (microscopy and toluidine blue staining), mitochondrial function (mitochondrial membrane potential; JC-1 staining), mitochondrial reactive oxygen species (ROS) (MitoSOX dye), proliferation (MTT assay) and viability (Annexin-V/propidium iodide staining).
Results: Primary human PTEC (n=4) cultured under low-dose oxidizing conditions displayed reduced proliferation and increased cell death compared with PTEC cultured alone. This effect was further amplified under high-dose oxidizing conditions. Mitochondrial deficit and ROS production were increased under oxidising conditions. ACEi delivered with H_2O_2 improved % of cell proliferation (MTT assay, approximately 65% of controls with 0.4mM H_2O_2 to 85% with ACEi plus H_2O_2). Similarly, membrane potential indicated by JC-1 staining showed improvement with ACEi.
Conclusions: Use of primary human PTEC for in vitro models of CKD is likely to produce more relevant data than kidney cell lines that in general are made up of transformed cultures. Our data suggest that PTEC respond to oxidative stress in a manner similar to pathogenesis of CKD in human patients, and that use of Enalapril improves CKD parameters. We will test whether any synergy is present between established CKD therapies such as Enalapril and plant-derived extracts currently in use against CKD. Thus we have established a pre-clinical human model of CKD for future assessment of novel bioactive (anti-oxidant) compounds as adjunct therapies to conventional medicines and ultimately translation into clinical testing in CKD patients.

SAT-198

SIGNIFICANT URINARY METABOLITES IN THE PROGRESSION OF CHRONIC KIDNEY DISEASE

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Introduction: Despite the development of diagnostic techniques, methods for predicting changes in renal function or outcomes are still insufficient. Metabolomics is considered to be a breakthrough method to address the shortage of tools by analyzing the end metabolites, reflecting genetic and environmental factors. Herein, we would like to propose the metabolites which significantly associated with development and progression of chronic kidney disease (CKD).
Methods: We measured urinary metabolites from 1,274 urine samples at the time of renal biopsy and 147 urine samples from healthy subjects using nuclear magnetic resonance. The clinical outcome was defined as a decrease in estimated glomerular filtration ≥ 30%, doubling of serum creatinine, or development of an end-stage renal disease.
Results: Initial partial components analysis and partial least squares-discriminant analysis score plots showed discriminated cluster between CKD and control, and according to the stage of CKD. A total of 41 metabolites confirmed to candidate marker associated with CKD. We took survival analysis by the median value of each metabolite. There were 9 metabolites (acetone, betaine, choline, dimethylamine, fumarate, glycerol, lactate, leucine, trimethylamine-N-oxide) which showed significantly increased risk of developing clinical outcomes according to increasing concentration. In contrary, citrate, and glycine showed decreased risk according to increasing concentration for developing clinical outcomes. Total of 8 metabolites (betaine, choline, fumarate, trimethylamine-N-oxide, lactate, leucine, methyl histidine, citrate) revealed significantly different level in concentration in CKD compared to control, moreover this difference maintained with same way in a different stage of CKD.
Conclusions: Metabolites which inform the disease progression or development can be a noble biomarker. In our study, betaine, choline, fumarate, trimethylamine-N-oxide, lactate was revealed as a significant predictor in the progression of CKD. Although additional study for validation should be performed, we could find significant metabolites associate with CKD. And these results could be an instrumental keynote to moving ahead.

SAT-199

ASSOCIATION BETWEEN SERUM LIPID PROFILES AND PROGRESSION OF CKD: KNOW-CKD STUDY

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Introduction: Dyslipidemia has been linked to an increased risk of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). However, the role of individual lipid parameter in the development of in the progression of CKD is not well established.
Methods: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 1,939 patients who measured total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were included in the analysis. Study endpoint was a composite of a ≥ 50% decline in estimated glomerular filtration rate or the onset of end-stage renal disease.
Results: The mean age was 53.8 ± 12.2 years and 1,192 (61.5%) patients were males. The mean serum concentrations of TC, LDL-C, HDL-C, and TG were and 174.1 ± 38.9, 96.9 ± 31.3, 49.3 ± 15.5, and 156.6 ± 96.9 mg/dl, respectively. During a median follow-up of 3.0 years, 421 patients (21.7%) reached the composite end point. In the fully adjusted multivariable Cox models, HDL-C was significantly associated with increased risk of CKD progression (HR, 1.11 per 10 mg/dl increase; 95% CI, 1.01-1.22; P = 0.03), while TC (HR, 0.99 per 10 mg/dl increase; 95% CI, 0.95-1.03; P = 0.53), LDL-C (HR, 1.01 per 10 mg/dl increase; 95% CI, 0.97-1.06; P = 0.68), and TG (HR, 0.99 per 10 mg/dl increase; 95% CI, 0.98-1.01; P = 0.35) were not. However, areas under the curve of these 4 lipids were similar and none of the parameters did not improve the net reclassification improvement and the integrated discrimination improvement for the progression of CKD.