Conclusions: Prior studies suggesting that Black PWH have lower risk than White individuals for early CKD progression but higher risk at later stages were likely biased by the race coefficient. Assigning higher kidney function for all Black individuals based on race systematically masks a subgroup of Black PWH who are at higher risk of CKD progression.

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TH-OR67

GFR in the Era of Precision Medicine: The Importance of a Measured GFR in Onco-Nephrology
Francesco Trevisani,1 Giulia Pegoraro,2 Daniele Pugno,2 Giulia Quattrini,1 Federico Di Marco,3 Alessandra Cinque,1 Arianna Bettig,1 Umberto Capitani,2 Andrea Salonia,1 Giorgio Pizzagalli,1 Francesco Montoroi,1 IRCCS Ospedale San Raffaele, Milano, Italy; 2Biorek S.R.L., Milano, Italy.

Background: An accurate assessment of renal function in nephropathological patients (pts) is of paramount importance. Unfortunately, the most used method to measure GFR is represented by the estimated GFR(eGFR) which harbours a significant error in comparison to gold standard(mGFR). Aim of this study was to determine the extent of the error of eGFR compared to the mGFR in onco-nephrological pts.

Methods: A total consecutive cohort of 200 pts was collected to compare the eGFR formulas (MDRD, CKD-EPI 2012) with mGFR method(Iohexol Plasma Clearance). Cohort composition: 116 oncological pts(cases) and 84 functional diseases pts(controls) matched for baseline variables. The agreement between eGFR and mGFR was evaluated using bias, precision, accuracy, and total deviation index. The differences between cohorts were evaluated with Fisher’s exact test and Chi-squared test and Wilcoxon rank sum test for continuous variables.

Results: Clinical data are reported in Table 1. The two matched cohorts displayed no statistical differences in term of clinical variables and agreement parameters(TDI, TDI, CCC and P30). Surprisingly, both groups harboured a non negligible errors in each CKD class with a huge discrepancy between the eGFR formulas and the gold standard method (Figure 1, 2), suggesting the great relevance of mGFR in the clinical decision making algorithm, both with two and one kidney.

Conclusions: The error in the classification of CKD stages using eGFR by formulas was too common in case and controls, with a poor agreement with mGFR in all CKD classes. The use of mGFR should be mandatory to obtain a tailored management in onco-nephrology.

Figure on the left represent the percentages of pts with four different intervals of error. Figure on the right represent the classification of pts in CKD stages by eGFR. True positive represent subjects that were correctly classified from eGFR and false positive represent the cases that were not classified in the corresponding class. Table shows the clinical data of the population divided in two cohorts: functional and oncological pts.

TH-OR68

The Effect of Age on Performance of the Kidney Failure Risk Equation in Advanced CKD
Gregory L. Hundemer,1 Navdeep Tangri,2 Manish M. Sood,3 Ayub Akbari,1
1Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2University of Ottawa, Ottawa, ON, Canada; 3University of Manitoba, Winnipeg, MB, Canada.

Background: The Kidney Failure Risk Equation (KFRE) is a validated clinical tool used to predict progression from CKD to kidney failure. Concerns over risk overestimation have been raised with prediction models, such as the KFRE, where death is not treated as a competing event. Herein, we evaluated the effect of age (with which the competing risk of death would be anticipated to increase) on KFRE performance in advanced CKD.

Methods: All patients referred to the advanced CKD clinic at the Ottawa Hospital from 2010-2018 were divided into age quartiles: <58, 58-67, 68-77, and ≥78 years. Predicted vs observed rates of kidney failure were compared over 2- and 5-years. Predictive performance of the KFRE was determined by ROC curves (discrimination) and calibration plots. Cumulated incidence of kidney failure was compared between models that accounted for the competing risk of death and those that did not.

Results: The mean (SD) age and eGFR were 66 (15) years and 17 (8) ml/min/1.73m². The median (IQR) 2- and 5-year KFRE scores were 20% (11-30%) and 81% (55-96%), respectively. The KFRE overestimated the risk of kidney failure among the oldest age quartile (≥78 years) with absolute differences of 5.8% (P=0.01) and 21.6% (P=0.001) between predicted and observed risks over 2- and 5-years, respectively. The 2-year KFRE discrimination was reduced among patients ≥78 years compared with patients 58-67 years (P=0.03) and 68-77 years (P=0.03) though the difference was non-significant when compared with patients <58 years (P=0.06). The KFRE displayed adequate calibration across all age quartiles. The cumulative incidence of kidney failure was overestimated in models that did not account for the competing risk of death and this overestimation was more prominent with older age.

Conclusions: In older patients with advanced CKD at high risk of kidney failure, the KFRE overestimates risk and this overestimation relates to the increasing competing risk of death with older age.

TH-OR69

A Prediction Equation for Incident CKD Using Routinely Collected Data: The Kidney Disease Risk Equation (KDRE)
Manish M. Sood,1 Stephanie Dixon,2 Emily Rhodes,1,2 Ottawa Hospital Research Institute, Ottawa, ON, Canada; 3Institute for clinical and evaluative sciences, London, ON, Canada.

Background: The identification of individuals at risk for incident CKD (eGFR < 60 ml/min, stage 3a) is an important first step for disease surveillance, monitoring, education and allocation of key therapies to reduce CKD progression. Despite recommendations, albuminuria measurements in appropriate individuals remains poor. As such, we set out to develop and validate a prediction equation for new onset CKD with and without an albumin creatine ratio (ACR).

Methods: Population-level administrative data cohort of 1,109,905 adults (>66 years old) from Ontario, Canada April 1, 2008 and December 31, 2017 with a minimum of 2 eGFR measures (one for baseline > 70 ml/min, one for outcome) were included. Prediction equations stratifying individuals with (n=191,690) and without (n=998,255) ACR were derived, internally validated by bootstrapping and externally validated in 122,148 (22,809 ACR, 99,335 non-ACR) individuals in Manitoba, Canada. The study outcome was a single eGFR measure < 60 ml/min/1.73 m² with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min and a single eGFR < 45 ml/min as study outcomes.

Results: Among individuals (54.5% women, mean age 64 SD 7, mean baseline eGFR 82 SD 8, median ACR 1 IQR 1-3), an eGFR < 60 ml/min occurred in 37.2% during the follow-up. The final model including up to 6 variables (age, sex, baseline eGFR, hemoglobin, time from hypertension and diabetes mellitus diagnosis) yielded a 5-year c-statistics of 0.77 (no ACR) and 0.78 (with ACR) with excellent calibration. Model performance was similar in additional analyses and in an external validation.

Conclusions: An equation incorporating readily available and routinely collected administrative data variables can accurately predict the onset of CKD with or without ACR.

TH-OR70

Tubular Secretion of Creatinine and Clinical Outcomes: The AASK Trial
Pratyay S. Garmimela,1 Kevin M. Cummins,3 Jennifer J. Gassman,2 Francine B. Gabbi,1 Joachim H. IX,1 1University of California San Diego, La Jolla, CA; 2Cleveland Clinic, Cleveland, OH; 3California State University Fullerton, Fullerton, CA.

Background: Tubular secretion is a critical kidney function that is not routinely assessed. We evaluated the association of tubular secretion of creatinine calculated using the difference between either measured glomerular filtration rate (mGFR) or estimated GFR (eGFR) and 24-hour urine creatinine clearance (CrCl) with long-term clinical outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: This prospective analysis of the African American Study of Kidney Disease and Hypertension (AASK) included 990 participants with baseline measures of ischemic mGFR, creatinine based eGFR and 24-hour urine Ccr. Tubular secretion of creatinine was calculated in two ways as the difference between 1) CrCl and mGFR (mTS<sub>c</sub>), and 2) CrCl and eGFR (eTS<sub>c</sub>). The associations between mTS<sub>c</sub> and eTS<sub>c</sub> with incident end-stage kidney disease (ESKD), cardiovascular disease (CVD) and all-cause mortality were evaluated using Cox regression. Results: At baseline, the mean mGFR was 45.3 ml/min/1.73 m<sup>2</sup>, and the mean CrCl was 49.3 ml/min/1.73 m<sup>2</sup>. The mean (SD) mTS<sub>c</sub> and eTS<sub>c</sub> were 4.0 (14) and 6.5 (14) ml/min/1.73 m<sup>2</sup>. Over a 4.2 years of follow up there were 149 ESKD, 82 all-cause mortality, and 132 incident CVD events. Each 10 ml higher mTS<sub>c</sub> was associated with lower risk of ESKD, after adjustment for mGFR or eGFR, proteinuria, and other potential confounding factors (Table). Associations between mTS<sub>c</sub> or eTS<sub>c</sub>, with lower risk of all-cause mortality or CVD events were not detected. Conclusions: eTS<sub>c</sub> provides a measure of creatinine secretion similar to mTS<sub>c</sub> and is strongly associated with risk of ESKD, independent of GFR, proteinuria, or other risk factors. This allows for the incorporation of eTS<sub>c</sub> into epidemiological studies which may have collected mGFR.

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FR-OR01

Role of Off-Target Ferrochelatase Inhibition in Vemurafenib Nephrotoxicity
Josie A. Silvaroli, Ji Young Kim, Navjot Singh P. Pabla. The Ohio State University, Columbus, OH.

Background: Complications linked with both cancer and anti-cancer therapeutics can trigger kidney injury. For targeted anti-cancer therapeutics, nephrotoxicity may occur because of on- or off-target mechanisms. In melanoma and other cancers with BRAF kinase activating mutations, targeted small molecule therapeutics such as vemurafenib, and dabrafenib have shown remarkable clinical benefits. However, recent clinical studies have shown that a significant number of patients that receive vemurafenib develop AKI through mechanisms that remain unknown. Here we have developed cell culture and murine models of vemurafenib nephrotoxicity to understand the causal mechanisms.

Methods: We established a murine model of vemurafenib toxicity through oral administration of 20 mg/kg vemurafenib in C57BL/6J mice. We confirmed kidney damage and toxicity in these mice through measurement of blood urea nitrogen, serum creatinine, histological analysis, and TUNEL staining. Using the GGT-Cre strain we have also generated BRAF conditional knockout mice. To understand the role of ferrochelatase we used a hydrodynamic siRNA injection approach or heterozygous (+/fch) mutant mice. Control and gene knockout mice were treated with vemurafenib to examine the role of ferrochelatase (FECH), an enzyme involved in heme biosynthesis contributes to renal injury is warranted.

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FR-OR02

Kidney Tubule Polyploidization Is an Evolutionary Conserved Mechanism Required to Survive AKI
Letizia De Chiara, Carolina Conte, Maria Lucia Angelott, Giulia Antonelli, Anna J. Peired, Maria elena Melica, Benedetta Mazzigni, Laura Lasagni, Elena Lazzeri, Paola Romagnani. Universita degli Studi di Firenze, Firenze, Italy; Azienda Ospedaliero Universitaria Meyer, Firenze, Italy.

Background: Acute Kidney Injury (AKI) is characterized by a rapid deterioration of kidney function. Recently, we showed that tubular epithelial cells (TEC) respond to AKI by triggering polyploidy, a condition in which a normally diploid cell acquires additional sets of chromosomes. Polyploidy offers several advantages, but in the kidney the biological significance of polyploidization remains unclear. In this study we hypothesized that polyploidy 1) is the predominant cellular response during AKI and 2) is an adaptive stress response required to maintain a residual kidney function to assure survival.

Methods: To address these hypotheses, we employed in vivo transgenic models based on the Confetti reporter and the Fluorescence Ubiquitin Cell Cycle Indicator (Fucci) technology in combination with YAPI downregulation. Mice were subjected to unilateral ischemia reperfusion injury (IRI) or glycerol-induced rhabdomyolysis to induce AKI. Polyploid cells have been then characterized by single-cell RNA sequencing analysis, cell sorting, FACS analysis, super-resolution and transmission electron microscopy.

Results: After AKI, YAPI is activated driving TEC polyploidization. Polyploid TEC increase in parallel to massive cell death triggered by AKI suggesting that polyploidization could be a means to escape cell death. Indeed, we found that polyploid TEC tend to accumulate genome instability and survive, while diploid TEC do not. Of note, virtually all dying cells were cycling based on the Fucci reporter suggesting that TEC death occurred during the S or G2/M phase. As polyploid TEC increase immediately following AKI, they may be required to survive injury and damage by sustaining renal function. In order to evaluate the functional role of polyploid cells during AKI, we generated YAPIko mice, where YAPI is knock-out specifically in TEC. Indeed, after AKI, YAPIko mice showed a reduced number of polyploid cells, worsened kidney function and a dramatic reduction of mouse survival, proving that polyploidization is required to survive AKI.

Conclusions: In conclusion, we demonstrated that after AKI: 1) TEC accumulate genome instability and die or become polyploid; 2) TEC polyploidy is essential to preserve residual kidney function allowing survival.

FR-OR03

Single-Cell and Spatial Transcriptomics Reveal Distinct Subpopulations of Kidney Resident Macrophages in AKI
Matthew B. Chung, Elise Erman, Jerome M. Lever, Anupam Agarwal, James F. George. The University of Alabama at Birmingham, Birmingham, AL.

Background: Macrophages are important in renal homeostasis and the response to acute kidney injury (AKI). Kidney resident macrophages (KRM) are a unique, self-renewing F4/80<sup>+</sup>CD11b<sup>+</sup> population that originate from the fetal yolk sac and fetal liver during embryogenesis. Preliminary data suggests that the KRM population consists of a number of undescribed subpopulations with distinct functions, but the transcriptional signatures and spatial organization of these subsets in the kidney tissue remain unknown. Here, we combined scRNAseq and spatial transcriptomics to identify and localize KRM subpopulations during homeostasis and injury.

Methods: Fluorescence activated cell sorting was used to isolate KRM from C57BL/6J mice without treatment and at one and six days after bilateral ischemia-reperfusion injury (IRI). Single-cell RNA sequencing was performed using the 10X Genomics platform. For spatial transcriptomics, kidney sections were placed on 10X Vismap Spatial Gene Expression slides, imaged, and then sequenced. scRNAseq and spatial expression data were integrated and analyzed using the R package, Scenius 4.0.

Results: UMAP plots of integrated data from injured and control mice revealed 6 major clusters of KRM with unique transcriptional profiles. Spatial transcriptomics revealed that these clusters reside in distinct cellular compartments within the kidney. Following IRI, these subpopulations appear in cellular compartments distinct from those occupied in the controls. Gene ontology analysis (Biologic Process) indicated that the largest subpopulations changing location expressed transcripts associated with locomotion and chemotaxis. It also indicated that the transcriptional profiles of each subpopulation were associated with distinct functions.

Conclusions: Transcriptionally distinct subpopulations of KRM resides within specific kidney microenvironments and change location as a function of injury. Gene expression data suggests that they are physically migrating from one compartment to another and indicates that resident macrophages in the kidney are not static with respect to transcriptional profiles and location. Therefore, further study of the temporal and spatial characteristics and signaling pathways of these subpopulations in the context of homeostasis and injury is warranted.

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