P0056 **USE OF CLINICAL EXOME SEQUENCING IN THE DIAGNOSTIC FLOW OF MONOGENIC KIDNEY DISEASES: THE PIEDMONT EXPERIENCE**

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Background and Aims: next-generation sequencing (NGS) technologies are becoming a powerful diagnostic tool in precision medicine. Specifically, exome sequencing can help in the diagnosis of selected diseases, in their medical management and therapeutic choices. Inherited kidney diseases (IKD) are among the major causes for kidney failure, both in children and adults, resulting in increased mortality, high health care costs and need for organ transplantation. In addition, it is worth mentioning that a significant proportion of patients in the kidney transplant lacks a clear diagnosis. This subset of diseases may thus benefit from the application of NGS technology, as the simultaneous investigation of hundreds of genes can lead to the identification of causative variants in a vast population of patients.

The aim of this study is to validate the use of a clinical exome sequencing approach in the diagnostic flow for kidney diseases leading to organ failure to i) confirm the clinical diagnosis, ii) find the genetic cause of previously unrecognized diseases and iii) improve the outcome of organ transplantation by excluding live-donors carrying the same mutational burden.

Method: 160 patients were recruited, directly or following a genetic counseling, exploiting a network of 21 nephrology centers spread across the Piedmont region, coordinated by the "Centro Regionale Trapianti (CRT)" of Torino. Patients were then evaluated for NGS eligibility. DNA extracted from blood samples was checked for integrity, quantified and used for library preparation. A clinical exome sequencing (CES) kit by Illumina was used, allowing for targeted capture, enrichment and sequencing of 6700 clinically relevant genes. Reads were aligned to hg37 reference genome using the Isaac enrichment tool and variants filtered using an *ad-hoc* set up pipeline of analysis.

Results: clinical exome sequencing was performed on a diagnostic cohort of 138 patients, both children (37.7%) and adults (62.3%), with a prevalence of male subjects (56.5%). The majority of the cohort (51.5%) presented a positive family history for kidney disease, while 22 patients were excluded from the study as organ failure was most likely the result of secondary events. The cohort was highly heterogeneous with 21% of patients presenting with ciliopathies, 18.1% with glomerular disease, 7.2% with tubular disease while the remaining cohort presented other diseases or was undiagnosed (44.3%). An *ad hoc* analytical pipeline was designed, based on selected genotype-phenotype correlation database, filter-in metrics, inheritance model and annotation of variants based on public databases and *in-silico* prediction tools. By adopting well defined criteria of recruitment and analysis, causative genes were identified in 61.6% of cases and in the 57.3% of cases results were in line with the original diagnostic hypothesis. Moreover, 50.8% of cases with organ failure for unknown reasons were solved with the identification of causative genes. Out of the 133 total variants found in the cohort, 63 were classified as pathogenic or likely pathogenic. The remaining 70 identified variants were annotated as variant of unknown significance and will be further investigated.

Conclusion: Taken together, these results show that CES is a powerful non-invasive tool for the genetic diagnosis of IKD. Identification of disease causative variants may represent a critical step for the diagnosis, clinical management of the patients, and potentially for optimal live-donor selection.