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GARVAN INSTITUTE OF MEDICAL RESEARCH

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We are delighted to report on the completion of our project '*A novel genetic test for Autosomal Dominant Polycystic Kidney Disease*'. Our team at the Garvan Institute, including Prof John Shine, Dr Timothy Furlong, Dr Mark Cowley and Ms Yvonne Hort, collaborated with the PKD Group at the Mayo Institute, USA to achieve this outcome.

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic condition that affects about 1 in 1000 Australians. ADPKD is caused by mutations in one of two genes, *PKD1* or *PKD2.* The disease causes cysts to form in the kidney, that eventually overtake the normal kidney tissue and lead to kidney failure. Patients with kidney failure then require dialysis or kidney transplantation to survive. ADPKD is most commonly passed through families, such that an affected parent has a 50% chance of passing the condition to their children. There are many potential benefits in genetic testing in ADPKD, including to clarify diagnosis, for reproductive planning and for selecting living-related kidney donors. However, genetic testing in ADPKD is challenging. This is due to six non-functional pseudogenes that share almost 97% sequence homology with the *PKD1* gene and therefore confound most standard sequencing methods. Our group previously reported on the first application of Whole Genome Sequencing (WGS) to diagnose ADPKD. We wanted to build on these results with the aim of developing an accredited genetic test for ADPKD in Australia.

The aim of this project, with the help of the PKD Foundation of Australia, was to validate WGS as a diagnostic test for ADPKD. This was achieved by blindly comparing results in a cohort of ADPKD patients who had previously been sequenced by more established methods (Long-Range PCR and Sanger Sequencing of *PKD1* and *PKD2).* We partnered with the Mayo Clinic in the United States, who provided us with samples of 30 patients who had previously been sequenced by Long-Range PCR and Sanger Sequencing of *PKD1* and *PKD2*. The Mayo Clinic also performed sequencing in 12 patients who had undergone WGS at the Garvan Institute. Sequencing, variant analysis and interpretation was performed in a blinded fashion. We found that the results were concordant (the same) between the two sequencing techniques in 40/42 samples. In two samples, WGS did not readily identify mosaic variants, as variant filtering had been targeted for detection of heterozygous (50:50) variants. Importantly, WGS was able to define the breakpoints of multiple large deletions, which had only been roughly detected by previous MLPA methods.

We concluded that our WGS method had comparable diagnostic rates to Long-Range PCR and Sanger Sequencing, but requires less laborious laboratory preparation and is able to better detect deletions, duplications and structural variants. Importantly, these results were a valuable step in accrediting the first diagnostic genetic test for ADPKD in Australia, which is now available through the Garvan Institute's diagnostic laboratory, Genome.One. Improved access to genetic testing allows patients to better understand the disease in their own family. Importantly, more comprehensive sequencing techniques can assist in improving our understanding of the genetic basis of ADPKD, which is an important step in identifying potential treatments.

Many thanks to the PKD Foundation of Australia for supporting our project.