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Nationwide diagnostic yield of clinical genomics in patients with suspected genetic kidney disease

Abbreviated authors: Jayasinghe K, Quinlan C, Mallett AJ on behalf of the Australian and Melbourne Genomics Renal Genetics Flagships part of the KidGen Collaborative

Full list of authors:
Alexander S[2,3], Bennetts B[2], Boudville N[4], Boughtwood T[1], Chakera A[4], Chalinor H[5], Chaturvedi S[6], Crafter S[7], Creighton B[8], Faull R[9], Fowles L[10], Haan E[9], Hunter M[13], Huntley V[9], Jayasinghe K[8,11], Johnstone L[8], Jose M[12], Kellett S[7], Krzesinski E[13], Larkins N[14], Lunke S[15], MacShane M[16], Mallawaarachchi A[17], Mallett A[1,18,19], Martyn M[20], McCarthy H[2,3], Mincham C[14], Nicholls K[21], Pachter N[16], Parasivam G[22], Parmar J[17], Patel C[10], Prawer Y[8], Quinlan C[23,24], Rangan G[25], Ryan J[8], Stark Z[1,15], Sundaram M[6], Talbot A[21], Tchan M[26], Torronen S[7], Trainer A[21], Trnka P[27], Uebergang E[5], Valente G[5], Wallis M[5,12], Wardrop L[1,24], West K[21], White SM[15], Whitlam J[5], Wilkins E[15]

1. Australian Genomics Health Alliance
2. The Children's Hospital at Westmead, NSW
3. The University of Sydney, Westmead, NSW
4. Sir Charles Gairdner Hospital, WA
5. Austin Hospital, VIC
6. Royal Darwin Hospital, NT
7. Women's and Children's Hospital, SA
8. Monash Medical Centre, VIC
9. Royal Adelaide Hospital, SA
10. Genetic Health Queensland
11. Monash University, VIC
12. Royal Hobart Hospital, TAS
13. Monash Genetics, VIC
14. Perth Children's Hospital, WA
15. Victorian Clinical Genetics Service, VIC
16. Genetics Services of Western Australia, WA
17. Royal Prince Alfred Hospital, NSW
18. Royal Brisbane and Women's Hospital, QLD
19. University of Queensland, QLD
20. Melbourne Genomics Health Alliance, VIC
21. Royal Melbourne Hospital, VIC
22. The Sydney Children's Hospital Network, NSW
23. Royal Children's Hospital, VIC
24. Murdoch Children's Research Institute, VIC
25. Westmead Institute for Medical Research, NSW

26. Genetic Medicine, Westmead Hospital, NSW
27. Queensland Children's Hospital, QLD

Background: With increased understanding of genetic kidney disease (GKD), genomic testing is translating from research to clinic. Rigorous evaluation of clinical practice and patient outcomes is required to guide value-based healthcare. We aimed to describe diagnostic outcomes of clinically accredited genomic testing delivered by nationwide multidisciplinary team (MDT) clinics for patients with suspected GKD.

Methods: Sequential incident patients undergoing clinically indicated genomic testing for presumed GKD from 18 Australian MDT clinics 2016-19 were analysed (HREC/16/MH/251). A molecular diagnosis constituted clinical reporting of pathogenic and/or likely pathogenic variant/s in gene/s associated with the patient kidney phenotype with concordant inheritance. All genomic testing included restriction of variant analysis to a phenotype derived gene list. Full author list online at KidGen.org.au.

Results: Of 824 patients, 52.1% were female. Median age was 26 years. A molecular diagnosis was made in 43.7%. A further 15.4% had a variant/s of uncertain significance (VUS), of which 23.6% were clinically compelling but require further functional validation or additional segregation. The diagnostic yield for whole genome (WGS n=92, 41.3%), whole exome (WES n=231, 40.7%) and clinical exome (CES n=392, 42.3%) sequencing was similar (p=0.91). Median age at test request for WGS (42yrs) was significantly older (p<0.00001) than WES (27yrs) and CES (18yrs). Of all patients with a genetic finding, 53.6% involved variation in 7 genes (COL4A3, COL4A4, COL4A5, PKD1, PKD2, PKHD1, HNF1B). Stratifying by age at test request, the diagnostic rate was not significantly different between 0-15yrs (41.8%), 16-25yrs (48.5%) and 26+yrs (44.2%) (p=0.25). The gender mix in these age groups was significantly different (female 45.8% vs 51.5% vs 56.7%, p=0.015).

Conclusion: Clinical genomics delivered by MDT clinics are diagnostically effective for suspected GKD. Neither sequencing approach nor age group at test request appear to impact diagnostic yield though WGS patients in this cohort were older and gender mix changed with increasing patient group age. Clinical utility studies are required to clarify impact of these diagnostic outcomes.