KI REPORTS
KIReports.org

Genetic Kidney Disease Across the Lifespan – Emerging Insights From Clinical Genomics in Older People

Kathleen Nicholls[1,2] and Andrew J. Mallett[3,4,5]

[1]Department of Nephrology, Royal Melbourne Hospital, Parkville, Victoria, Australia; [2]Department of Medicine University of Melbourne, Parkville, Victoria, Australia; [3]Department of Renal Medicine, Townsville University Hospital, Douglas, Queensland, Australia; [4]College of Medicine and Dentistry, James Cook University, Douglas, Queensland, Australia; and [5]Institute for Molecular Bioscience, The University of Queensland, St Lucia, Queensland, Australia

Kidney Int Rep (2025) **10,** 2548–2550; https://doi.org/10.1016/j.ekir.2025.06.050

See Clinical Research on Page 2140

The growth in understanding of genetic kidney disease has burgeoned over the past several decades. This has been punctuated by key moments of reflection and discovery, leading to an increasingly sophisticated knowledge of gene and disease relationships. In the recent past, this has been enabled and accelerated substantially by the implementation of genomic technologies, first in research and now in clinical practice.[1,2] With increased accessibility and uptake[3] have come important insights, including those recently presented by Elhassan *et al*.[4] The longstanding perception that human disease of a monogenic etiology is primarily prevalent within pediatric populations was also the initial impression in nephrology. Genetic kidney disease is now, however, being demonstrated to be a diagnosis of potential interest for people affected by kidney disease of all ages,[5,6] now clearly including those of older age. This is perhaps because of the inherent diversity of phenotypes, inheritance patterns, multigene interactions, and lifespan dynamics that are becoming characteristic of genetic kidney disease (Figure 1).

Elhassan *et al*.[4] report the diagnostic yield of diagnostic genomic testing in a cohort of 265 adults aged ≥ 60 years from 202 families in Ireland. The high proportion (74%) progressing to kidney failure at a median age of 62 years is a highly clinically relevant end point. Overall, 60% of families and 55% of patients with disease onset at or after the age of 60 years had a diagnostic variant identified. Although the perception has historically been that this would be predominantly because of a high proportion of cystic kidney disease, the diagnostic yield in non–cystic kidney disease families was still comparably high at 39%. Important factors of a positive

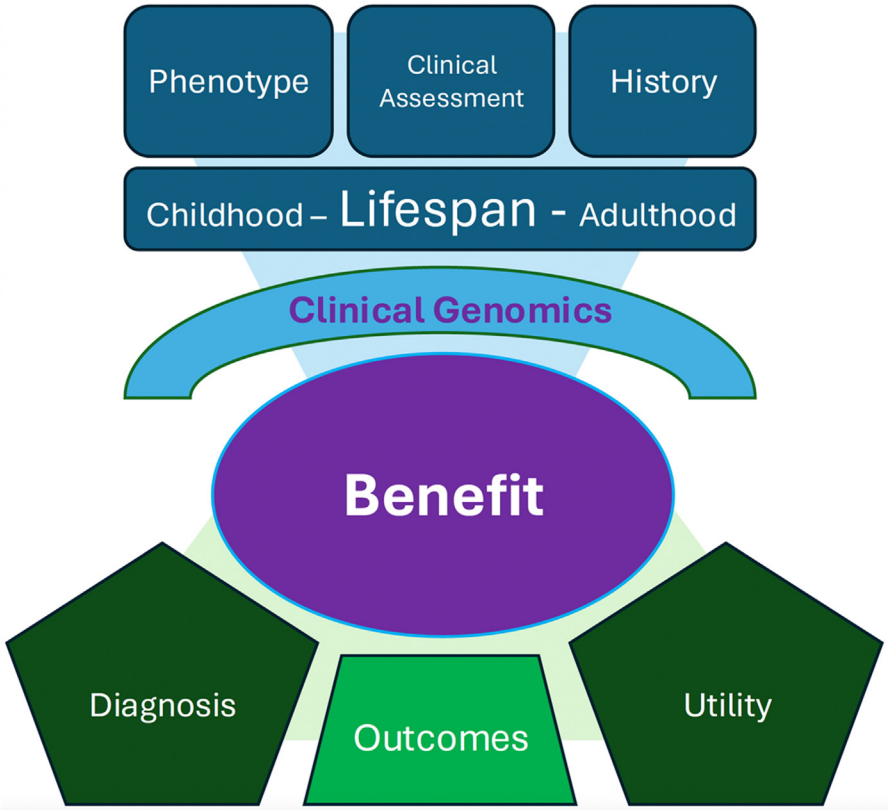

Figure 1. Lifespan model of genomics in suspected genetic kidney disease.

Correspondence: Andrew Mallett, Department of Renal Medicine, Townsville University Hospital, Douglas, Queensland 4814, Australia. E-mail: Andrew.mallett@health.qld.gov.au

family history of chronic kidney disease or *a priori* cystic kidney disease were significant, though not exclusive predictors of a positive genetic result. Although the landscape of genetic etiologies was different to younger groups, there was still the observation that approximately a quarter of older adults with positive genetic test results subsequently received modified treatment plans. There are 4 domains in which these results are both important and thought provoking.

First, though there has been some perception of monogenic disease as having been of greater relevance in pediatric and/or younger age groups, this is now broadening to a whole of lifespan appreciation. The very significant genetic diagnostic yield persisting across adulthood,[7] all the way to older ages of adulthood, is highly relevant. This is in and of itself clinically important to appreciate and reframes clinician expectations of the patient group in whom a monogenic diagnosis might be considered and a diagnostic genomic test performed. There are, however, some differences that add nuance. For instance, in this study, the genetic etiologies found in this older cohort were those associated with later-onset phenotypes, including cystic kidney disease (*PKD2, IFT140, ALG5, ALG9,* and *DNAJB11*), glomerular disease (*COL4A5* in females and monoallelic *COL4A3*) and tubulointerstitial disease (some *UMOD* variants). This leads to an appreciation that many of these are monoallelic disorders and mostly inherited in a dominant fashion.

The appreciation of persistent but different monogenic findings in older adulthood leads to a second thought provoking moment where one considers that though onset would appear later, in combination with dominant inheritance and high diagnostic yield, this results in a more nuanced landscape of potential clinical benefits and utility. As has come to be expected, a very high proportion (95%) of patients with a genetic diagnosis experienced utility in the form of a change in their individual treatment plan. The largest contributors to this though were cascade familial testing (74%) and familial genetic counselling (54%). Personal utility in terms of treatment plan modification (24%) was also observed, in addition to appreciable aspects such as disease prognostication (27%) and kidney transplantation elements (15%), where despite less time opportunity because of older age, significant utility was still identified. All together this illuminates that rather than there being potentially lesser utility in this older age group, there is in fact likely just as much utility, even if that utility is composed differently. This accords with recent reports of broad factors underpinning priority indicators and valuation of utility in rare disease.[8,9] A substantial take-home point is the potential to derive demonstrable utility when there are family members of younger age who are at risk for later onset genetic kidney disease phenotypes.

Third, the findings of Elhassan *et al.*[4] bring into focus the emerging theme of genetic kidney disease as a disease spectrum of relevance across nearly all pediatric and adult nephrology. Previous reports have established the likely and expected prevalence in adult groups with increasing thresholds at which older age has had evident benefit.[3,6] Here, this is now well-established and so nephrologists should be encouraged to incorporate family history taking, careful phenotyping, and thoughtful diagnostic considerations for all patients at all ages who might present for evaluation and kidney care.

Fourth and perhaps most pointedly, there now opens a discussion around questions of equity. Now, older age should no longer be thought of as a factor which is contrary to the potential expectation of a diagnostic outcome with genomic testing if monogenic kidney disease is potentially present. With increasing access and availability to genomic testing, this implores us to ensure that not only are we providing diagnostic testing and interventions that are well-reasoned and evidence-based, but also that empower patients and families. Although this work in and of itself will not resolve many of the patient inequities currently or historically present in kidney health, this is a positive step toward ensuring that important questions and research are undertaken, to test boundaries and assumptions in the pursuit of illuminating how to optimally progress patient management. Older patient age should no longer intrinsically be a potential barrier or negative factor toward considering genomic testing in the diagnostic process toward achieving an etiological answer.

In summary, Elhassan *et al.*'s[4] novel work has further and iteratively revealed just how important and prevalent monogenic forms of kidney disease are. The positive impact of an accurate etiological diagnosis is important in a multitude of ways, including conclusion of diagnostic odysseys, provision of high-quality clinical management, and patient-centric care. The potential psychologically positive impacts for patients and families from a genetic diagnosis in terms of subjective relief, avoidance of blame, and obviation of stigma is also important to

consider. Just as powerful and precise new diagnostic tests such as clinical genomics become available, it is evidence such as the work of Elhassan *et al.*, which is critical to inform their quality use to ensure maximized benefit and interpretation.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the patients who participated in the studies referenced. AJM is supported by a Queensland Health Advancing Clinical Research Fellowship.

AUTHOR CONTRIBUTIONS

KN and AM drafted the manuscript with all coauthors providing input, review, and edits.

REFERENCES

1. Stark Z, Byrne AB, Sampson MG, et al. A guide to gene-disease relationships in nephrology. *Nat Rev Nephrol*. 2025;21:115–126. https://doi.org/10.1038/s41581-024-00900-7
2. Mallett AJ, McCarthy HJ, Ho G, et al. Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders. *Kidney Int*. 2017;92:1493–1506. https://doi.org/10.1016/j.kint.2017.06.013
3. Elhassan EAE, Murray SL, Connaughton DM, et al. The utility of a genetic kidney disease clinic employing a broad range of genomic testing platforms: experience of the Irish Kidney Gene Project. *J Nephrol*. 2022;35:1655–1665. https://doi.org/10.1007/s40620-021-01236-2
4. Elhassan EAE, Cormican S, Osman SM, et al. Characterization of monogenic kidney disease in older patients with CKD. *Kidney Int Rep*. 2025;10:2140–2152. https://doi.org/10.1016/j.ekir.2025.04.017
5. Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int*. 2019;95:914–928. https://doi.org/10.1016/j.kint.2018.10.031
6. Jayasinghe K, Biros E, Harris T, et al. Implementation and evaluation of a national multidisciplinary kidney genetics clinic network over 10 years. *Kidney Int Rep*. 2024;9:2372–2385. https://doi.org/10.1016/j.ekir.2024.04.068
7. Bensouna I, Doreille A, Dancer M, et al. Nephrogenomics, precision medicine and the role of genetic testing in adult kidney disease management. *Nat Rev Nephrol*. Forthcoming 2025.
8. Fehlberg Z, Goranitis I, Mallett AJ, et al. Determining priority indicators of utility for genomic testing in rare disease: a Delphi study. *Genet Med*. 2024;26:101116. https://doi.org/10.1016/j.gim.2024.101116
9. Goranitis I, Sheen D, Fehlberg Z, et al. A standardized measurement and valuation scale of genomic utility for policy decisions: the GUV scale. *Value Health*. 2025;28:184–190. https://doi.org/10.1016/j.jval.2024.11.014