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Missing in Plain Sight No More? Copy Number Variation in Monogenic Kidney Disease

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Recent findings from Claus *et al.*[1] have illuminated, at scale, the contribution that copy number variants (CNVs) make to monogenic forms of kidney disease. Whereas previous reports have predominantly focused on the diagnostic yield of genomic sequencing in terms of single nucleotide variants,[2,3] this report demonstrates that approximately 3% of all patients undergoing diagnostic genomic testing for suspected monogenic kidney disease harbor a CNV contributing to diagnostic yield. Alternatively, this can be viewed through the lens that 1 in every 10 genetic diagnoses reported were attributable to a CNV. This information is critical for the design, update, and implementation of contemporary diagnostic genomic sequencing approaches for monogenic kidney disease.

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There are several key strengths to this study and aspects which are worth considering. The cohort size is large with the majority able to undertake CNV analysis using the primary whole exome sequence (WES) data. As a clinically accredited genomic pipeline, quality control steps were in place with a small number of cases unable to proceed with WES-based CNV analysis. Other methodologies such as chromosomal microarray or multiplex ligation-dependent probe amplification were however required, alone or in combination with WES-based CNV analysis, highlighting the need for proactive thought and planning for individual cases and scenarios. Further, this frames well the real-world aspect of this large study (n = 2432 patients) over a substantial period (approximately 8 years) during which significant evolution of genomic sequencing technologies and genomic diagnostics has occurred. In many ways, this report demonstrates the benefits of a learning health system approach to clinical and precision medicine, whereby key learnings are iteratively generated and then integrated into practice.

Therefore, the generalizability of this study is likely to be extensive with high degrees of relevance to the practice of nephrogenetics and genomics across many jurisdictions globally. Further, this fundamental knowledge about CNV contributions to diagnostic yield has generalizability into the genomic analysis workflows of both research and clinical pipelines within contemporary nephrology. Although there might be multiple clinical models of care and multidisciplinary care being explored, this critical information will be of broad applicability across scenarios and extends into further evolution and nuance of genetic counselling in nephrology.

There are also key learnings about the knowledge and skill set of both nephrologists and genetic clinicians. For example, for nephrologists this information is of relevance to informing the core curriculum of the evolving subspecialty in genetic kidney disease and nephrogenetics. Whereas previously, most learning has focused on the identification of relevant gene-phenotype relationships and single nucleotide variant identification and curation, further evidence-informed ongoing education is now indicated regarding the approach to considering and identifying CNVs. This will be important for kidney clinicians in terms of their intrinsic knowledge and understanding of the genomic testing that they might be requesting, but also for their pretest and posttest counselling of patients in the contexts of informed consent and result disclosure.

At this point in the evolution of diagnostic genomic technologies, this new evidence is of critical relevance both generally but also within specific clinical scenarios and disorders. For instance, whereby previously dedicated consideration of a potential causative CNV may have been required to activate a specific sequencing approach, such as chromosomal microarray or multiplex ligation-dependent probe amplification, this can now instead be in many instances undertaken in almost routine fashion as part of a single diagnostic genomic analysis pipeline. One example of this is 17q12 microdeletions[4] as part of the spectrum of *HNF1b*-related nephropathies and disorders in which chromosomal microarray is required to detect the potential CNV in addition to other sequencing for single nucleotide variants. Another example is *CFHR5* nephropathy[5] in which there is a specific duplication of exons 2 and 3 of *CFHR5* traditionally requiring multiplex ligation-dependent probe amplification to identify this CNV. Furthermore, this paper highlighted the capability of CNV in identifying complex structural rearrangements in established genes such as *COL4A4*.

Although some specific approaches may still be required in some clinical circumstances, for many, a more unified approach is likely now achievable, as Claus *et al.*[1] have demonstrated, in which consideration of CNV detection tools are integrated with traditional single nucleotide variant detection and reporting workflows (Figure 1). It is important to note that at present, many diagnostic genomic workflows in nephrology utilize capture-based or WES as the core sequencing methodology,[6] and this highlights the need for strong quality control and assurance processes to both maximize performance and the ability to apply CNV detection tools, as well as to avoid inadvertent nondetection of variants.[7] With whole genome sequencing however demonstrating system level evidence[8] and some early clinical implementation in nephrology[9] one looks towards a future state where whole genome sequencing based diagnostic genomic testing will enable a more comprehensive initial approach to undertake and a more robust platform for iterative genomic reanalysis and thus time-based growth in diagnostic yield.

In the immediate future and until evidence emerges about relative cost-effectiveness and cost-benefit of whole genome sequencing rather than WES, a pragmatic response to this new evidence of a significant contribution of CNVs to diagnostic yield in instances of suspected monogenic kidney disease should prevail. For the 1 in 10 such patients in whom a genetic diagnosis might be realized, this is highly likely to enable substantial personal and family benefits from conclusion of the diagnostic odyssey. And where might this lead in terms of the clinical care and treatment that can be offered? It might be too early to predict; however, as a first tenet, we are unlikely to be able to treat what we do not understand. In this instance, understanding is likely to flow from achieving an accurate diagnosis.

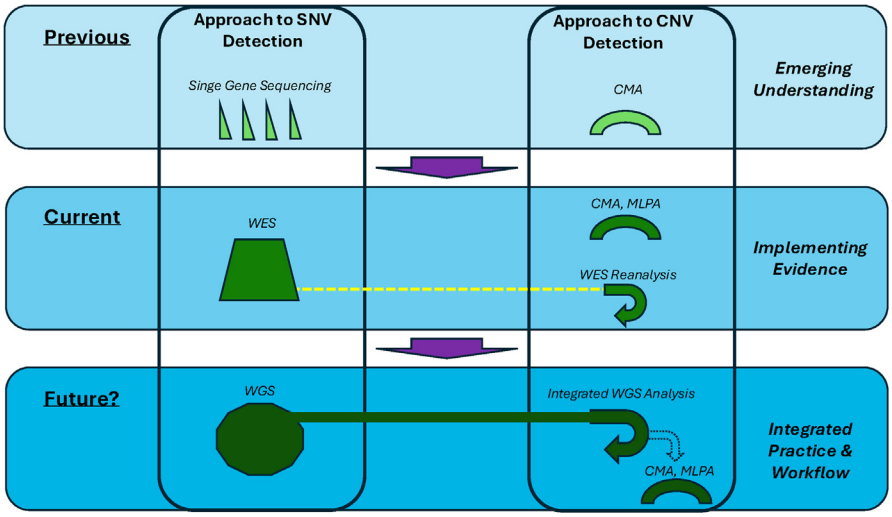

Figure 1. Evolution of diagnostic genomic workflows to incorporate copy number variant identification and reporting. CMA, chromosomal microarray; CNV, copy number variant; MLPA, multiplex ligation-dependent probe amplification; SNV, single nucleotide variant; WES, whole exome sequencing; WGS, whole genome sequencing.

DISCLOSURE

All the authors declared no competing interests.

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Author Contributions

JJ and AM conceptualized the editorial after invitation from the journal. JJ and AM drafted the manuscript with both providing input, review and edits.

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