Clinical versus research genomics in kidney disease

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Clinical versus research genomics in kidney disease

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Key differences exist between clinical and research genomics. As genomic testing is adopted in nephrology clinical care, we propose focusing on clinical genomics approaches to obtain genetic diagnoses in order to ensure optimal use of resources and maximum patient benefit.

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Genomics is transforming kidney research[1] and has begun to transform clinical care[2,3]. However, the core differences between clinical and research genomics must be understood to enable translation, engage clinicians, meet patient expectations and address ethical concerns[4].

Clinical genomic testing

The aim of clinical genomic testing is to answer a specific clinical question[5], typically when an underlying genetic disorder is suspected based on clinical presentation, investigation results and/or family history (FIG. 1). A genomic diagnosis might be sought in the hope of providing a confirmed or precise diagnosis, prognostic information and information to guide treatment, amongst other potential positive outcomes. However, genomic testing can produce results that are negative, uncertain or incidental and could have broad impacts on health insurance and psychosocial wellbeing as well as on family members and relationships. Before undergoing genomic testing, the patient, and in some instances their family, should receive pre-test counselling from a qualified professional with relevant experience.

To enable optimal interpretation of the results of clinical genomic testing, the requesting clinician must communicate a detailed phenotype to the diagnostic laboratory team, preferably using standardized terminology such as the Human Phenotype Ontology (HPO). In many instances, involvement of the requesting clinician in multidisciplinary variant assessment and reporting functions is advantageous for clinically-focused data interpretation.

Results from clinical genomic tests are returned to patients within clinically meaningful timeframes ranging from days to months. The results form part of the health-care record and can be used to inform the clinical management of the tested individuals and their relatives, impacting decisions on long-term, complex and costly treatments, including kidney transplantation both for potential recipients and living related donors. Results can also impact personal decisions such as reproductive plans. Thus, clinical genomic tests must be held to high standards of external clinical accreditation by an accountable standards body (for example Clinical Laboratory Improvement Amendments (CLIA) or the International Organization for Standardization (ISO)). Such accreditation ensures end-to-end veracity from informed consent to sample collection, sequencing, data analysis, variant curation, confirmation, reporting and genetic counselling. Individual steps in this sequence must also adhere to clear criteria such as the American College of Medical Genomics and Genetics variant classification guidelines[6] and to processes designed to maintain clinical purpose such as restricting analyses to genes with established clinical validity. These standards underpin confidence in the clinical status of identified variants and their subsequent use to inform clinical care.

Research genomic testing

Research genomics is targeted at research outcomes with incidental potential clinical benefits (FIG. 1). The research goals frequently focus on identifying and characterizing novel disease genes and improving the understanding of how genetic variation contributes to health and disease[7]. Testing may be performed on prospectively obtained samples or on samples that were obtained with broad research consent from patients and healthy volunteers. The testing might not be related to the primary reason why a participant entered a study and the results might not be returned to participants. The study methodologies can vary and might include the latest sequencing or analysis platforms and bioinformatics pipelines that are experimental or have not been validated. Results frequently take months or years to evaluate and the findings are interpreted within a research setting with a discovery or exploratory mindset, where the use of terms such as 'mutation' or 'disease-causing' may be used more loosely than in a clinical setting. Whether the individual results of genomic research studies, including or excluding incidental findings, should be disclosed to participants has been debated for decades and important ethical controversies and practical challenges remain. When results are returned to participants, they require clinical diagnostic validation before they can form part of the medical record and be used to inform patient care.

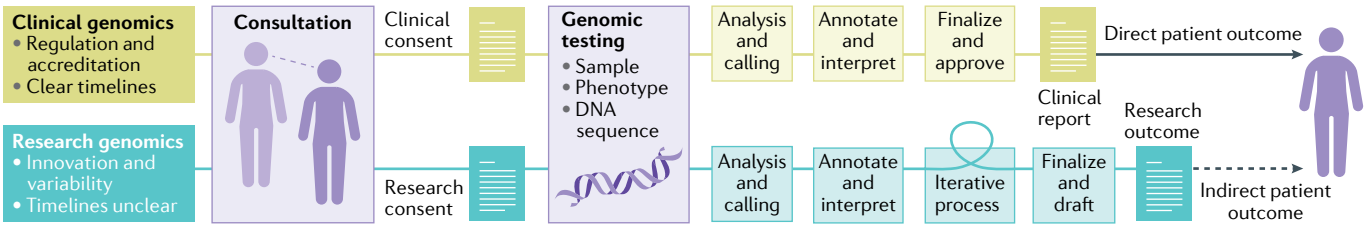

Fig. 1 | **Comparison of research and clinical genomics.** Key differences between research and clinical genomic pathways include type of consent, regulation and accreditation, variability in study methodologies, timelines for reporting results and whether outcomes are communicated to patients. Importantly, those who undertake an initial clinical pathway that does not result in a diagnostic outcome can subsequently pursue research pathways.

> Research genomics is targeted at research outcomes with incidental potential clinical benefits

A shared way forward

Genomic testing is rapidly transitioning from the research to the clinical environment with many governments investing heavily to accelerate the integration into health care[8]. Translational projects in which genomic testing is performed within a clinical framework[9,10] are key to the evaluation of patient and family outcomes, such as diagnostic and clinical utility, as well as cost effectiveness to inform planning of health-care services and to identify the barriers to and enablers of effective implementation. During the next 5 years, genomic data from over 60 million patients are expected to be generated within health care[8]. These data are likely to originate disproportionately from high-income countries and particular effort will be required to address under-representation of global genomic and population diversity, which has the potential to increase health inequities. As the promise of genomics becomes a reality for both kidney medicine and research, the international success of both endeavors relies upon clear definitions and delineation.

The current understanding of monogenic and oligogenic forms of kidney disease is incomplete. The interplay of research genomics, functional genomics (that is, modelling of genetic variants in model systems) and clinical translation is of key importance to enable improvements in clinical care and patient outcomes. The immense volume of data generated from clinical and research genomics might enable various types of secondary use. Substantial potential exists for research to be undertaken in clinical settings owing to opportunities arising from the use of whole exome or genome sequencing as first or second tier genetic tests, which might identify novel variants and genes that require further interpretation.

> We propose focusing on clinical genomics as a primary medium for obtaining a genetic diagnosis

In a clinical context, secondary use of data might involve iterative reanalysis as new genomic understandings emerge. In the research setting, these data may enable scaled and iterative research to advance understanding of health and disease in ways that have not been previously possible, including interrogation of deep intronic alleles, repetitive regions, synonymous alleles and regulatory regions. In both instances, clinical value and utility will depend on the efforts of clinicians and researchers to iteratively integrate such findings into practice over time. Furthermore, systems must be in place to support patients and families in undertaking informed consent, which is key to enabling such translation.

We propose focusing on clinical genomics as a primary medium for obtaining a genetic diagnosis whenever possible. This approach should facilitate active participation of patients in shared decision-making, including via emerging approaches such as dynamic informed consent. When undertaken with a common set of values encompassing clinical diagnosis, transparency, efficiency and research enablement, such an approach is predicted to provide a platform for contemporary practice. Focusing on clinical genomics also represents an optimal use of limited clinical and research resources whilst ensuring maximum patient benefit in the short and long term.

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Competing interests
The authors declare no competing interests.

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