



Genetic Counseling in Nephrology: Challenges and Opportunities

Abstract

Genetic testing is increasingly used in nephrology to diagnose hereditary kidney diseases, guide therapy, and inform transplant decisions. However, integrating genetic data into routine care presents ethical, logistical, and psychosocial challenges. This review outlines the key elements of genetic counseling in nephrology, including testing modalities, informed consent, legal and regulatory frameworks, and interpretation of complex results. In the Indian setting, rapid growth in genetic testing outpaces current policy and infrastructure, raising concerns about data privacy, cost, and protection from genetic discrimination. As genomic medicine continues to expand, nephrologists have an important role in advocating responsible testing practices and supporting patients through complex genetic information.

Keywords: Genetic counseling, Genomic medicine, India, Hereditary kidney diseases, Nephrology

Introduction

Genetic testing is increasingly used in the evaluation of patients with suspected hereditary kidney disease. A study on pediatric patients using clinical exome sequencing reported an overall diagnostic yield of 46%.¹ In adults, international studies have identified positive genetic tests in 20-40% of patients with CKD.^{2,3} The impact extends to therapeutic strategy - such as immunosuppression tailoring - and to transplant planning, where identifying mutations in potential living donors refines risk assessment. Furthermore, detection of a disease-causing variant in a patient facilitates cascade testing among at-risk relatives, enabling early monitoring and preventive interventions. Advances in next-generation sequencing (NGS) have dramatically expanded access to genetic testing. Yet alongside this clinical utility lies a number of ethical, logistical, and psychosocial challenges. These include risks of genetic discrimination, navigating incidental findings, and communicating genetic risk to relatives. This review outlines key components of genetic counseling in nephrology, including testing modalities, informed consent, data privacy, and management of uncertain findings. In India, the rapid expansion of genetic testing outpaces current policy, creating opportunity and obligation for clinicians to advocate for responsible genomic care.

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Testing Modalities

The diagnostic yield of genetic testing depends both on the underlying variant type and the choice of sequencing method.

Sanger sequencing

Sanger sequencing remains a gold-standard technique for detecting single-nucleotide variants (SNVs) and small insertions or deletions (INDELS) within specific genes or targeted regions. This method uses fluorophore-labeled dideoxynucleotides (ddNTPs), which lack a 3' hydroxyl group, thereby terminating DNA elongation when incorporated. Repeated cycles of primer binding and DNA synthesis result in fragments of varying lengths, which are separated via capillary electrophoresis and analyzed based on their fluorescent tags. Although its clinical use has decreased with the advent of NGS, Sanger sequencing remains valuable for targeted applications, such as confirming variants identified through NGS, sequencing technically challenging regions, or testing specific genes in at-risk family members.

Targeted NGS/Curated gene panels

NGS, also known as massively parallel sequencing, enables high-throughput sequencing of millions of DNA fragments simultaneously, offering greater speed and reduced cost compared to Sanger methods. In nephrology, curated gene

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panels designed to assess a selected set of genes associated with kidney disease are commonly employed. DNA is fragmented, regions of interest are enriched via probe hybridization or PCR, and sequencing libraries are constructed using sample-specific adapters. Following sequencing, reads are aligned to a reference genome and analyzed to identify clinically relevant variants. Several commercial laboratories offer panels tailored for nephrology and related specialties.

Whole exome sequencing (WES)

WES extends the capabilities of NGS by sequencing the exome, the protein-coding portion of the genome that comprises only 1-2% of total DNA but harbors the majority of known pathogenic variants. It is often utilized in research or in clinical cases where targeted panels have not yielded a diagnosis. While WES can detect variants missed by gene panels, its broader scope increases the likelihood of encountering variants of uncertain significance (VUS). WES is not commonly available as a routine clinical test and may require referral to research-based or specialty programs.

Other options

Whole genome sequencing (WGS) offers comprehensive analysis by sequencing both coding and noncoding regions of the genome. However, its use in clinical nephrology is limited due to cost, data complexity, and limited availability. Chromosomal microarray (CMA) is another diagnostic tool that detects large-scale chromosomal abnormalities, such as copy number variations (CNVs). CMA is particularly useful in the evaluation of patients with structural renal anomalies or syndromic presentations, such as congenital anomalies of the kidney and urinary tract (CAKUT).

The Process and Challenges of Informed Consent

Informed consent is a foundational element of genetic counseling and testing, ensuring that patients are adequately prepared for the potential outcomes and implications of their results. The process involves a thorough discussion of the possible medical, psychological, financial, and familial consequences of testing.⁴ In some regions, written informed consent may be legally required prior to testing. As genetic testing becomes increasingly routine in clinical practice, the breadth and complexity of the data generated have challenged traditional models of consent. Key elements of the informed consent process are discussed below.

Legal requirements

Laws governing genetic testing and counseling vary widely across countries and even within regions, reflecting differing levels of regulatory maturity and ethical oversight. In India, as in many countries, formal legal requirements specific to clinical genetic testing remain limited, though evolving. The Clinical Establishments Act of 2010 mandates registration and adherence to standards related to staffing, infrastructure, and record-keeping for facilities offering

diagnostic services, including genetic testing.⁵ Genetic counseling is recommended, though not legally mandated, in the clinical setting. The Indian Council of Medical Research (ICMR) provides nonbinding but comprehensive guidance through its National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017), which recommend both pre-test and post-test counseling to ensure informed decision-making.⁶ From a data privacy perspective, the Digital Personal Data Protection Act (DPDPA) of 2023 classifies genetic information as sensitive personal data, requiring explicit patient consent for its collection, use, and disclosure.⁷ However, the DPDPA applies a uniform framework to all sensitive data types and does not include genetically specific safeguards, prompting concern that it may not fully account for the distinctive risks associated with the long-term identifiability and familial implications of genetic information.⁸

Genetic discrimination

India currently lacks comprehensive legislation specifically protecting individuals from genetic discrimination in employment or health insurance settings. While the DPDPA of 2023 recognizes genetic data as sensitive personal information requiring explicit consent for its collection and use, it does not prohibit the use of such information by insurers or employers, nor does it offer legal recourse in cases of discrimination. Unlike frameworks such as the U.S. Genetic Information Nondiscrimination Act (GINA), India does not restrict health or life insurance providers from using genetic test results when determining eligibility or premiums. As a result, patients undergoing genetic testing should be counseled on the potential implications of result disclosure, particularly when applying for private health, life, or disability insurance.

Cost

Genetic testing is not universally covered by government-funded health schemes or private insurance plans, and patients are often responsible for out-of-pocket expenses. When testing is performed through third-party commercial laboratories, some companies may offer fixed pricing structures or financial assistance programs to help reduce cost-related barriers.

Kidney donation

Genetic testing is increasingly being integrated into the assessment of prospective living kidney donors. When a pathogenic variant is identified, transplant teams must carefully weigh the penetrance and expressivity of the condition, along with the level of risk considered acceptable by both the donor and the clinical team. In the case of autosomal dominant polycystic kidney disease (ADPKD) caused by mutations in *PKD1* or *PKD2*, the development of renal cysts and progressive kidney dysfunction is highly penetrant and age-dependent, and such findings typically preclude donation. In other

contexts, such as with high-risk *APOL1* variants or mutations associated with Alport spectrum diseases, the decision-making process is more complex. These variants confer a variable and incompletely penetrant risk of kidney disease, and the absence of precise risk prediction models further complicates counseling. Such cases raise ethical challenges, requiring a careful balance between respecting the autonomy of a well-informed donor and the obligation of transplant teams to safeguard long-term donor health.

Return of Results Challenges

Secondary findings

Secondary findings refer to clinically significant genetic variants identified unintentionally during testing, outside the scope of the clinical indication for which the test was ordered. These may involve pathogenic mutations associated with conditions such as hereditary cancer syndromes, cardiomyopathies, or arrhythmia syndromes, where early detection may enable preventive interventions. Some international bodies, such as the American College of Medical Genetics and Genomics (ACMG), recommend the return of certain secondary findings - publishing a regularly updated list of genes considered actionable.⁹ There is currently no formal policy or consensus in India regarding their disclosure.

VUS

Genetic test results are interpreted using standardized classification systems that estimate the likelihood that a variant is pathogenic. Variants are typically categorized as pathogenic, likely pathogenic, uncertain significance, likely benign, or benign. While pathogenic and likely pathogenic variants are considered to have a deleterious effect on gene function and are used to inform clinical decision-making, VUS represent findings where the current evidence is either insufficient or conflicting to determine a clear relationship with disease. VUS findings are relatively common, particularly in populations that are underrepresented in reference genomic databases. These variants should not be used to assign risk, alter surveillance, or guide treatment, and patients must be appropriately counseled on their uncertain clinical implications. Notably, most VUS are eventually reclassified as benign as additional population and functional data become available.¹⁰

Psychosocial consequences

Genetic testing can have a range of psychosocial impacts, including anxiety, guilt, and strain on family relationships. Individuals may experience emotional distress upon learning they carry a pathogenic variant, particularly when this information has implications for their children or other relatives. Some may feel a sense of guilt about potentially passing on a heritable condition, while others may face pressure or conflict within the family regarding whether to pursue testing or how to disclose results. These issues can be especially complex in cultures where extended family dynamics and collective decision-making are prominent. Access to qualified genetic counseling can help patients

process these emotions, understand the implications of testing, and manage communication with family members in a supportive and informed manner.

Testing relatives of positive patients

Once a pathogenic variant is identified in an affected individual, it is considered standard clinical practice to offer genetic testing to at-risk family members - a process known as cascade testing. This approach is endorsed by kidney health organizations as a means of early detection and risk stratification.¹¹ However, testing of children introduces complex ethical and psychosocial considerations. Concerns include potential infringement on the child's future autonomy, the possibility of genetic discrimination, and the impact on family dynamics, particularly when unexpected findings, such as misattributed parentage, are revealed. In general, genetic testing in minors is recommended only when results would have immediate clinical utility, such as guiding surveillance or early intervention. In families where the implications for a child are uncertain, it may be more appropriate to first test other adult relatives to clarify inheritance patterns and estimate the child's risk indirectly.

Discussion

Genetic counseling is a critical component of incorporating genomic information into nephrology practice. As the availability of genetic testing expands in India, clinicians are faced with challenges around informed consent, interpretation of uncertain results, communication of familial risk, and protection of genetic privacy, often in the absence of robust regulatory frameworks. While international guidelines can provide a foundation, meaningful application requires contextual adaptation to local clinical practices, cultural norms, and healthcare infrastructure. As India moves toward broader integration of genomic medicine, nephrologists are well-positioned to lead in shaping ethically grounded, patient-centered care and in advocating for the development of policies that protect and empower individuals and families affected by genetic kidney disease.

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Use of Artificial Intelligence (AI)-Assisted Technology:

The authors declare that no generative AI or AI-assisted tools were used in drafting, editing, or preparing this manuscript.

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