GENETIC TESTING AND EMERGING THERAPIES FOR GENETIC KIDNEY DISEASES

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APPLICATIONS OF GENETIC TESTING IN KIDNEY DISEASES

We will introduce in this section what is genetic testing and therapy. Also, what is the current practice and benefits with regards to performing genetic testing in kidney diseases and what are the future directions of the field. We will also introduce in this section how does genetic testing help in managing patients with kidney disease.

EMERGING THERAPIES FOR GENETIC KIDNEY DISEASES

In this section, we will introduce emerging therapeutic strategies in the field of nephrology including ACE inhibitors and DNA editing for Alport's syndrome; the oral apolipoprotein L1 (APOL1) inhibitor, VX-147 for Focal Segmental Glomerulosclerosis; and the RNA interference (RNAi) agent, lumasiran for Primary oxaluria type 1.

DISCLOSURE:

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Definitions:

Genetic testing– the use of laboratory methods to examine an individual's DNA for variations typically performed in the context of medical care, ancestry studies or forensics. Results of a a genetic test can be used to confirm or rule out a suspected genetic disease and may also be used to determine the likelihood of parents passing on a genetic mutation to their children. [1]

Genetic therapy– technique that modifies a person's genes to treat or cure disease. This is done by either replacing a disease-causing gene with a healthy copy of the gene; inactivating a disease-causing gene that is not functioning properly; or introducing a new or modified gene into the body to help treat a disease. [2]

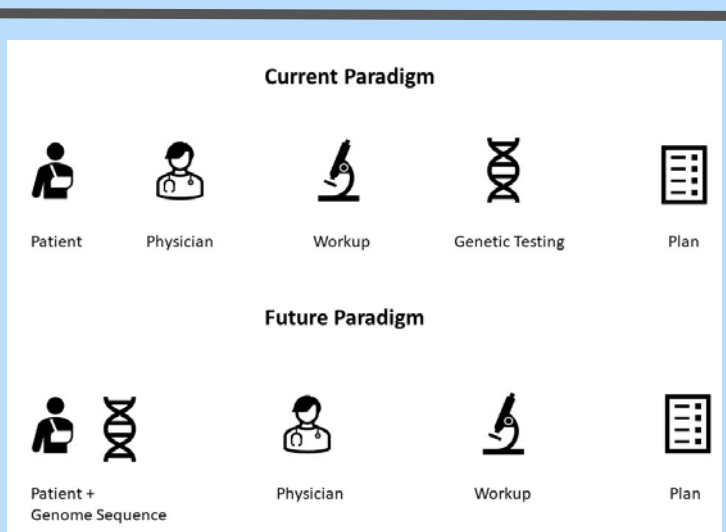

Figure 1. Current and Future Paradigm of Genetic Testing. Adapted from WCN 2022. Session- Genetics in CKD. Adult CKD: When to Consider Genetic Testing? by Dr Ali Gharavi. February 27, 2022.

"Genetic kidney disease may be present in at least 10% of CKD patients. Genetic testing can be used to personalize the diagnosis and management of kidney disease. In the near future, genomic information maybe acquired as an initial step in the patient visit," says Dr Ali Gharavi from his session on Genetics in CKD at the World Congress of Nephrology 2022. (Figure 1)

The 10% of CKD patients with genetic kidney diseases encompassed various diagnoses such as autosomal dominant diseases (67%) autosomal recessive diseases (14%) and X-linked diseases (18%). The findings of the study emphasized the high degree of genetic and phenotypic differences among hereditary nephropathies and show the extent to which genetic testing can be helpful to resolve clinical diagnostic challenges. [3]

EMERGING THERAPIES FOR GENETIC KIDNEY DISEASES

The rapidly developing applicability of genetic testing propels the development of new therapeutic agents for a number of genetic kidney disorders such as Alport syndrome, Focal segmental glomerulosclerosis (FSGS) and Primary oxaluria type 1 (PH1). In this section, we will give a brief overview of some study results for these therapeutic agents/strategies currently being developed for these disorders.

Alport syndrome (AS)

- The EARLY PRO-TECT study (n=66) showed a trend that ramipril could decrease disease progression (hazard ratio, 0.51; 95% CI, 0.12–2.20) and is safe to use (adverse event rate-ratio 1.00; 95% confidence interval [CI], 0.66-1.53). [4]
- Progress in the development of gene therapy for AS is currently limited to early testing and include employing mouse models using an inducible transgene system. Also, gene-editing technology using CRISPR (clustered regularly interspaced short palindromic repeats) is being investigated to target faulty genes in kidney cells. [5]

Focal segmental glomerulosclerosis (FSGS)

- A phase 2 study in patients with APOL1-mediated FSGS (n=13) demonstrated that the oral APOL1 inhibitor, VX-147 on top of standard of care achieved a statistically significant mean reduction of 47.6% (95 CI, 31.3–60) in the urine protein to creatinine ratio at week 13 compared to baseline. VX-147 was also well tolerated. [6]

Primary oxaluria type 1 (PH1)

- PH1 causes hepatic overproduction of oxalates leading to kidney stones, and kidney failure. The double-blind, phase 3, ILLUMINATE-A trial (n=39) demonstrated that the RNA interference (RNAi) agent, lumasiran significantly reduced urinary oxalate excretion vs. placebo (mean difference -53.5 % points; P<0.001) with normal oxalate plasma levels being achievable after 6 months of treatment. [7]

References:

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