Integrating genetic counselling into nephrology practice:

A primer for general nephrologists using the new MBS item numbers

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VCGS
leaders in genetic health

Outline

- Introduction to genetic counselling

- Genetic testing in nephrology
  - Why
  - Who
  - What
  - How

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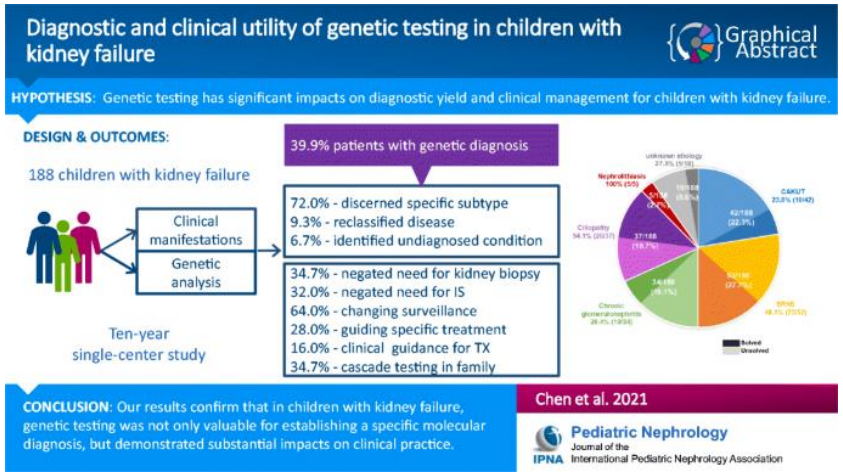
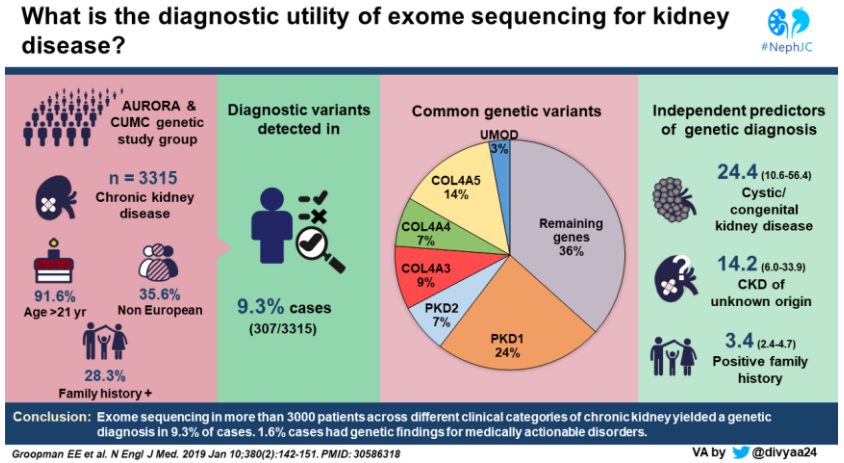
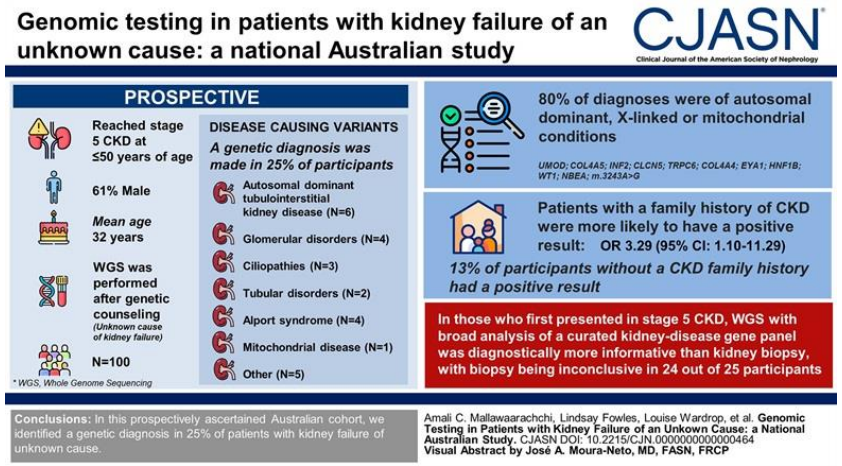
Stein, Q., Westemeyer, M., Darwish, T., Pitman, T., Hager, M., Tabriziani, H., Curry, K., Collett, K., Raible, D., & Hendricks, E. (2023). Genetic Counseling in Kidney Disease: A Perspective. *Kidney medicine*, *5*(7), 100668.

Why – diagnostic yield







Why – utility

Conditions amenable to specific disease-modifying therapies

Examples:
- *GLA* (Fabry)
- *AGXT* (primary hyperoxaluria [PH])
- CoQ10 genes (SRNS)
- *CTNS* (cystinosis)
- Tubulopathies (Na^+, K^+, etc.)

Conditions amenable to nonspecific renoprotective strategies

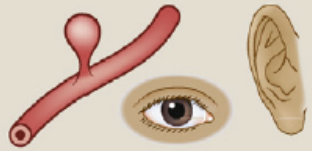
Example:
- *COL4A3/4/5* (Alport) and RAAS blockade

Avoidance of prolonged immunosuppressive therapies

Example:
- Glomerular disease due to mutations in Alport genes (*COL4A3/4/5*)

Conditions at risk for recurrence after kidney transplantation

Examples:
- (*CFH/CFI/C3..*): aHUS
- (*AGXT, GRHPR, HOGA*): primary hyperoxaluria (PH)
- Adenine phosphoribosyltransferase deficiency (APRT)



Conditions amenable to specific screening for extrarenal manifestations

Examples:
- *HNF1B*: diabetes
- *PKD1/PKD2* (ADPKD): intracranial aneurysms
- *FLCN*: renal cell carcinoma, etc.

Conditions for which genetic testing is relevant for reproductive counseling

Example:
- Prenatal/preimplantation diagnosis

KDIGO Conference Participants (2022). Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney international*, 101(6), 1126–1141.

Why – utility

Clinical impact of genomic testing in patients with suspected monogenic kidney disease

Melbourne Genomics Health Alliance

Methods & Cohort

4 tertiary hospitals in Melbourne, Australia

204 patients with clinically suspected GKD

Assessment in multidisciplinary Renal Genetics clinic and exome sequencing

Results

80/204 (39%) – diagnosis

47/80 (59%) – changed management

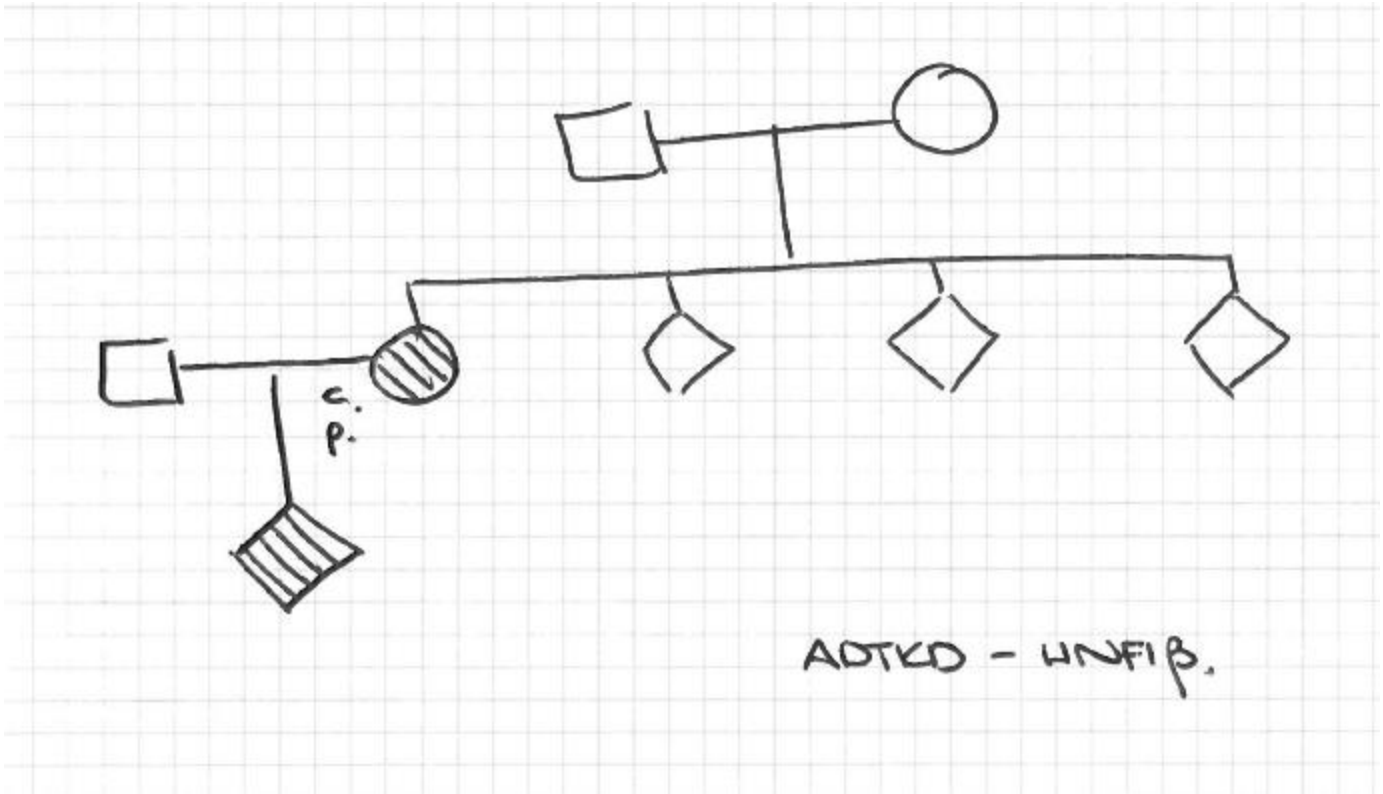
40/80 (50%) – informed cascade testing

- 35/80 (44%) changed surveillance
- 16/80 (20%) changed treatment
- 10/80 (13%) avoided biopsy

Younger age at presentation and positive family history was predictive of diagnosis through exome sequencing

Conclusions In a pediatric and adult cohort with suspected monogenic kidney disease, ES had high diagnostic and clinical utility. Our findings, including predictors of positive diagnosis, can be used to guide clinical practice and health service design.

Jayasinghe K, Stark Z, Kerr PG, Gaff C, Whitlam J, Martyn M, Creighton B, Donaldson E, Hunter Mathew, Jarmolowicz A, Johnstone L, Krzesinski E, Lunke S, Lynch E, Nicholls K, Patel C, Prawer Y, Ryan J, See E, Talbot Q, Trainer A, Tytherleigh R, Valente G, Walllis M, Wardrop L, West K, White S, Wilkins E, Mallett AJ*, Quinlan C*.
www.nature.com/articles/s41436-020-00963-4


c.
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ADTKD - HNF1β.

Genetic testing is standard of care

Genetic testing for heritable kidney disease

Last updated: 8 June 2022

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MBS eligibility

1. The patient is Medicare eligible
2. The episode of care is considered private
3. The patient's clinical presentation is consistent with the test eligibility criteria (as determined by the clinician)

- Relevant item numbers: 73298, 73299, 73401, 73402, 73403, 73404, 73405, 73406.

Who – identifying patients

- ✓ Young age of onset
- ✓ Positive family history
- ✓ Extra-renal features
- ✓ Parental consanguinity
- ✓ ESKD <50 with unclear aetiology

Jayasinghe, K., Stark, Z., Kerr, P. G., Gaff, C., Martyn, M., Whitlam, J., Creighton, B., Donaldson, E., Hunter, M., Jarmolowicz, A., Johnstone, L., Krzesinski, E., Lunke, S., Lynch, E., Nicholls, K., Patel, C., Prawer, Y., Ryan, J., See, E. J., Talbot, A., … Quinlan, C. (2021). Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genetics in medicine : official journal of the American College of Medical Genetics*, 23(1), 183–191.

Mallawaarachchi, A. C., Fowles, L., Wardrop, L., Wood, A., O'Shea, R., Biros, E., Harris, T., Alexander, S. I., Bodek, S., Boudville, N., Burke, J., Burnett, L., Casauria, S., Chadban, S., Chakera, A., Crafter, S., Dai, P., De Fazio, P., Faull, R., Honda, A., … Mallett, A. J. (2024). Genomic Testing in Patients with Kidney Failure of an Unknown Cause: A National Australian Study. *Clinical journal of the American Society of Nephrology : CJASN*, 19(7), 887–897.

How – which test?

Complexities of genetic testing

- Familial nature of information
- Uncertain results
- Unexpected findings (e.g. extra-renal features)
- Results can change with new information

Informed consent

1. About the test

It is my choice for the above-named patient to have genomic testing by panel/exome/genome analysis to look for changes in genes that may be associated with:

_____

Genomic test results are based on current knowledge, which may change in the future.

2. Potential outcomes

I understand:

- This test may find a cause for the condition(s).
- This test may not find a cause for the condition(s).
- The result may be of 'unknown significance', which means it cannot be understood today.
- There is a chance that genomic testing could find other medical conditions (incidental findings).
- This test will not predict all future health problems.
- Genomic testing may identify unexpected family relationships.
- Further testing or information sharing may be needed to finalise the result.

3. Results

I understand:

- I will be told the results by a health professional.
- I can choose not to be told about the results, but the report may still be included in the patient's medical record.
- Results may have implications for the health/genetic risks of the patient, and their family members.
- Results from these tests may affect the patient's ability to obtain some types of insurance.
- The results will be available to the team of health professionals involved in the patient's care.
- Results are confidential and may be released as specified in this form, or as allowed by law.

I give permission for the report to be shared with health professionals involved with the care of:

☐ all relatives of the patient ☐ specific relatives: _____

The following individual can be given the results, if I am unable to be contacted:

Name: _____ Contact number: _____

4. Data and sample sharing

I understand and agree that the sample, genomic data and related health information may be shared and stored to help advance scientific knowledge (in a de-identified format – that is, without personal identifiers such as name and address).

5. Research

I provide consent to share the sample, genomic data and related health information of the patient for ethically approved research into the same or a related condition, where it remains possible to re-identify the patient. This allows relevant information to be returned to me where appropriate. There may not be a direct benefit to the patient and their family.

☐ Yes ☐ No

6. Consent

I have had enough time to consider the information in this consent form and have:

- Had the opportunity to discuss genomic testing and its implications with a health professional.
- Been given access to information about genomic testing.
- Been able to ask questions until I am satisfied with the answers.
- Been offered a copy of this consent form.

I provide consent for genomic testing as summarised in this form.

Patient/Parent/Guardian signature: _____ Date: _____

Health professional signature: _____ Date: _____

Health professional name: _____

How to order a test

- Identify a testing laboratory
  - Must be NATA accredited to offer genomic testing
  - Sample requirements
  - Paperwork – pathology form, consent form

Disclosing the result

- Prepare in advance
- Preferably in person
- Consider language
- Identify patient resources
- Next steps

Interpreting results

Pathogenic / likely pathogenic variant

Variant of uncertain significance

No variants

Interpreting results

Pathogenic / likely pathogenic variant

- A genetic cause may have been identified
- Are there management implications?
- Are there implications for family members?

Interpreting results

- Not a diagnosis
- Insufficient evidence to classify variant
- May be reclassified in time / with additional evidence

Interpreting results

- A genetic cause has not been identified

- Technical limitations
- Incomplete genetic knowledge
- Non-genetic aetiology

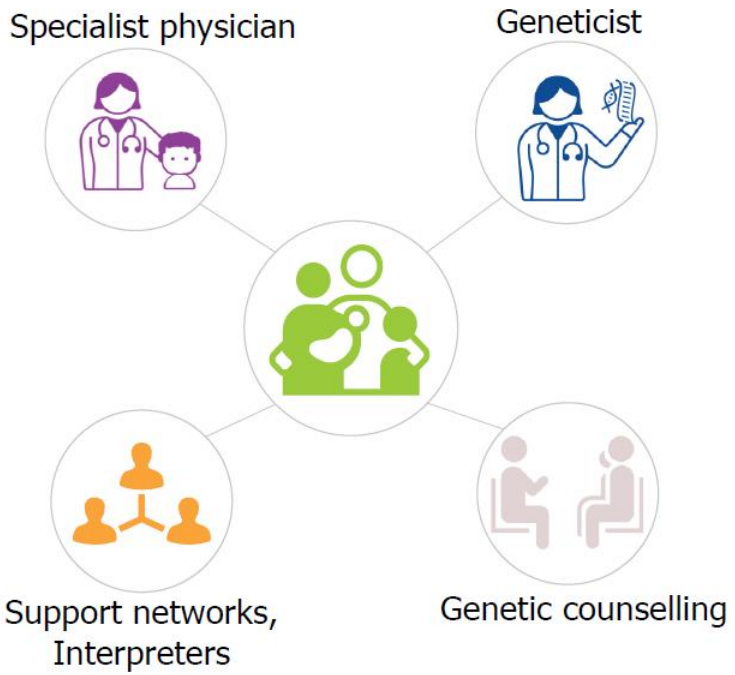
Other considerations

- Reproductive aspects
- Family members may be affected / at risk / healthy carriers
- How can your patient be supported to explain to their family members?

When to refer to genetics

- If additional testing is required to confirm / clarify the result
- Reproductive questions / family planning
- Testing for family members
- Grief / distress following result disclosure

Connect the dots - Experts, networks, support



Melbourne Genomics Health Alliance

Resources

Genomic testing for nephrologists:
www.kidneygenomics.org.au

Searchable list of genetics services:
www.genetics.edu.au

KidGen:
www.kidgen.org

Acknowledgments

- Melbourne Genomics Health Alliance
- Australian Genomics
- KidGen