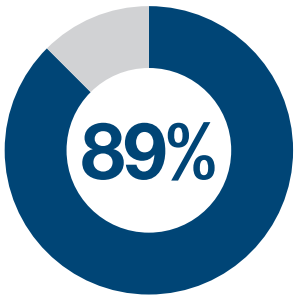
natera™ | Renasight™
Kidney gene panel

Clinical case series:
Target therapies or workup

Changing patient management with Renasight kidney gene panel



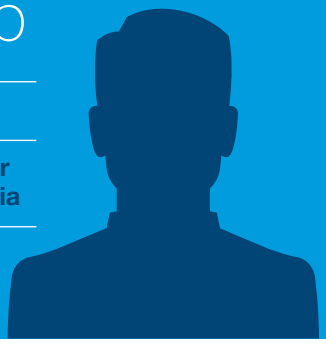
Renasight™ is a comprehensive kidney gene panel for patients with chronic kidney disease (CKD), electrolyte disorders, or nephrolithiasis.

A New England Journal of Medicine publication assessing the utility of DNA testing for kidney disease found that a genetic diagnosis had implications for clinical management in 89% of patients.[1] Highlighted are Renasight case studies that demonstrate how patient management and/or use of targeted therapies changed based on the genetic test results.

Meet Jacob

Late 20s

Presents for evaluation for nephrotic range proteinuria



History

- No family history of CKD
- Proteinuria since childhood
- Biopsy showed FSGS
- No response to Prednisone or ACTH gel
- Given atypical FSGS course and steroid resistance, additional immunosuppression deferred

Rationale for genetic test

- Clarify etiology of FSGS
- Understand benefit of additional immunosuppression
- Counsel on likelihood of future progression

Renasight Result

- Positive for *COL4A4*-related Alport Syndrome

Key Takeaway: Clinical Implications

No additional immunosuppression required

Remains at high risk for long-term renal disease progression

Very low risk for recurrence if patient requires transplantation

Known genetic etiology allows for informed family planning, identification of at-risk relatives

Identifies risk for hearing and vision deficits

Meet Angela

Late 50s

Referred for CKD stage 4T

History

- 2 kidney transplants
- Difficult to treat anemia
- Brother with kidney stones

Rationale for genetic test

- Evaluate for possible etiology of pancytopenia immediately after second transplant

Renasight Result

- Positive for *CFI*-related Atypical HUS

Key Takeaway: Clinical Implications

Patient could have avoided second kidney transplant altogether if the genetic diagnosis was known

Effective treatment with Eculizumab after second transplant

Meet Martin

Early 20s

End stage renal disease with unknown family history

History

- Unknown family history
- C3 deposition on kidney biopsy

Rationale for genetic test

- To gain all possible prognostic information prior to a transplant in patient with ESRD of unknown etiology

Renasight Result

- Positive for *NPHS2*-related Autosomal Recessive Nephrotic Syndrome Type 2

Key Takeaway: Clinical Implications

Transplant candidate as FSGS is unlikely to reoccur

Known genetic etiology allows for identification of at-risk relatives

Meet Sarah

Early 60s

Elevated creatinine

History

- No family history of kidney disease or autoimmune disease
- Generalized weakness
- Rheumatoid arthritis and sleep apnea
- Biopsy results: Focal necrotizing/crescentic and sclerosing pauci-immune (ANCA-associated) glomerulonephritis. Focal, mild tubular atrophy and interstitial fibrosis

Rationale for genetic test

- Unknown etiology of CKD

Renasight Result

- Positive for NR3C2-related Autosomal Dominant pseudohypoaldosteronism

Key Takeaway: Clinical Implications

Associated with mild salt wasting and hyperkalemia – improves with aging

Patient's electrolyte imbalances improved with steroids

Known genetic etiology allows for identification of at-risk relatives

Clinical case series: Target therapies or workup

Genetic testing results can provide information to tailor therapeutic strategies or work ups. Below are examples of how genetic testing results can inform patient management and treatment.

Disease Name	Gene	Therapeutic Application
Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)[2]	***UMOD, REN, HNF1B***	• ADTKD-UMOD | Gout: Prevention with allopurinol, febuxostat, or probenecid can be considered. Treatment with prednisone, short-term NSAIDs, or colchicine. • ADTKD-REN | Anemia: May be reversed by erythropoietin. Acute gout typically responds well to prednisone or colchicine. • Allopurinol may slow the progression of kidney disease • Kidney transplantation cures ADTKD-UMOD, REN, HNF1B.
CoQ10 Deficiency[3]	***COQ2, COQ6, PDSS1, PDSS2***	• Individuals with primary CoQ10 deficiency may respond well to high-dose oral CoQ10 supplementation (ranging from 5 to 50 mg/kg/day).
Fabry Disease[4]	***GLA***	• Enzyme replacement therapy (ERT) • Pathogenic missense variants can be treated with chaperone migalastat instead of ERT • Diphenylhydantoin, carbamazepine, or gabapentin to reduce pain • ACE inhibitors or angiotensin receptor blockers to reduce proteinuria
Primary Hyperoxaluria, Type 1[6] (PH1)	***AGXT***	• To reduce calcium oxalate supersaturation in the urine: maintenance of high fluid intake; inhibition of calcium oxalate crystal formation with potassium or sodium citrate, pyrophosphate-containing solutions.[5] • To reduce oxalate biosynthesis: pyridoxine supplements for those who are pyridoxine responsive • Discussion of avoiding carriers for this condition as combined liver and kidney transplant donors[7]
Renal Cysts and Diabetes Syndrome[8]	***HNF1B***	• Maturity-onset diabetes of the young (MODY): A minority respond to sulfonylureas. • Insulin is commonly needed. Anti-proteinuric agents and pancreatic enzyme supplements based on clinical presentation

References:
1. Groopman, E.E., et al., (2019). NEJM 380: 142-151. doi: 10.1056/NEJMoa180891
2. https://www.ncbi.nlm.nih.gov/books/NBK1356/ PMID: 11068651, 12205338, 19664745, 21084044
3. PMID: 25091424, 18579827, 22368301, 21540551, 10972372
4. PMID: 30601180, 11386930, 17483124, 19473999, 26937390, 17409308, 11439963, 17179052, 25795794, 17656478, 24886109,
5. https://pubmed.ncbi.nlm.nih.gov/20301460/
6. PMID: 15840016, 22547750, 22688746, 19571789, 10603104, 20301460, 8476723, 31580236, 30655312, 24776840, 23830800
7. https://www.ncbi.nlm.nih.gov/books/NBK1283/
8. https://www.ncbi.nlm.nih.gov/books/NBK500456/ PMID: 32864159, 16443774, 28420700

Learn more about Renasight:
Call us +1 650.425.4005
Visit us natera.com/renasight

201 Industrial Road, Suite 410, San Carlos, CA 94070 | Main +1 650.425.4005 | Fax +1 650.412.1974 | renasight@natera.com

natera™