Chronic Kidney Disease Gene Panels

Chronic kidney disease (CKD) is a condition characterized by gradual loss of kidney function over time.[1] Up to one-third of patients with CKD do not have a known underlying disease etiology.[2] In several recent studies of various methodologies utilizing genetic testing technology, it was found that between 12% and 56% of patients with idiopathic CKD were diagnosed with a monogenetic condition.[2] Patients are more likely to receive a diagnosis if they are of a young age at onset, have manifestations beyond the kidney, have a family history of kidney disease, or have an unusual disease course.[3,4]

The multigene panel allows for simultaneous sequencing of a pre-selected set of genes relevant to a disease phenotype.[2] The targeted phenotype-associated gene panels are used for the diagnosis of disorders with overlapping phenotypes or disorders with common pathways. Given this capability, gene panel technology can be applied to chronic kidney disease to elicit whether or not a patient harbors an underlying genetic etiology to their specific disease course. For the few genes that are unable to be studied with panel technology, other techniques can be used to fill in the gaps.

Fabry disease is a metabolic disorder, caused by pathogenic variants in *GLA,* that results in CKD in both males and females. Patients with Fabry can present with isolated CKD or with CKD in conjunction with additional signs and symptoms such as bradycardia, left ventricular hypertrophy, cardiac arrhythmias, heart failure, strokes, neuropathic and gastrointestinal pain, hearing loss, and angiokeratomas.[5]

Genetic Testing

Benefits of genetic testing include:[2]

- Potential to provide a diagnosis quickly through a minimally invasive manner
- Aids in early detection of extrarenal features and can help guide management
- Gives information about familial implications including recurrence risks, reproductive options, and targeted testing for at-risk family members

Recommendations for genetic testing in nephrology:[2]

- The patient should understand the benefits and limitations of genetic testing before agreeing to testing.
- Consider consulting with a genetics colleague. Genetics professionals can provide valuable insights regarding the following:
  - Interpretation of ambiguous results and incidental findings
  - Identification of at-risk family members and assist with cascade testing
  - Genetic counseling and disease management of extrarenal features of affected individuals

Fabry Disease

When a diagnosis of idiopathic CKD is present, ruling out a genetic etiology, such as Fabry, can shorten the diagnostic delay. The following evaluations may support a diagnosis of Fabry disease:[5]

Patient History	neuropathic pain, abdominal pain and diarrhea, hypohidrosis, fatigue, depression
Family History	premature stroke, renal failure, cardiomyopathy, sudden death
Examination	angiokeratoma, cornea verticillata, and hearing loss
Echocardiogram	left ventricular hypertrophy, hypertrophic cardiomyopathy
ECG	shortened PR interval (in early stages), bradycardia, AV-block, A-fib, T-wave inversion, NSVT
Cardiac MRI	late enhancement of posterior inferobasilar wall indicating myocardial fibrosis
Brain MRI	small vessel occlusion, dolichoectasia, white matter hyperintensities

For every patient diagnosed via clinical suspicion or screening, pedigree analysis identifies a mean of 5 family members with Fabry disease.[6]

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Laboratory Testing Options in Fabry Disease

Albuminuria, Proteinuria

- Males with baseline urinary protein <0.1 g/24 hr have an eGFR slope of -1.6 mL/min/1.73m^2/year compared with males with a baseline urinary protein >1 g/24 hr have an eGFR slope of –6.9 mL/min/1.73m^2/year [7]
- Females with baseline urinary protein <0.1 g/24 hr have an eGFR slope of –0.6 mL/min/1.73m^2/year compared with males with a baseline urinary protein >1 g/24 hr have an eGFR slope of –4.6 mL/min/1.73m^2/year [7]

Plasma or DBS lyso-GL3 (lyso-Gb3)

- Generally significantly increased in classic male patients[8]
- Elevated but less so in both non-classic males and classic females[5]
- May be mildly elevated or normal in non-classic female Fabry patients [5,8]

Kidney biopsy findings

- GL3 accumulation ("Zebra" or "myeloid" bodies) in multiple renal cell types[9]
- Podocyte injury prior to the emergence of overt albuminuria[9]
- Tubular atrophy; interstitial fibrosis; glomerularsclerosis[5]
- Microvascular endothelial GL-3 accumulation; arteriolar injury[5]

Genetic Testing Options

Sanofi does not review or control the content of non-Sanofi websites. These listings do not constitute an endorsement by Sanofi of information provided by any other organizations. The following is a selection of laboratories offering nephrology gene panels. This is not an exhaustive list of labs that offer one or the other or an endorsement of any one lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. To test individuals with a family history of Fabry for a known familial mutation, please contact your lab of choice to discuss. Content is current at time of printing and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics.

Lab	Panel Name (Test Code)	# of Genes	Sample Requirements	Kits	Avg TAT	Mobile Blood Draw	Genetic Counselor Available to Patients	Billing	Contact
CGC Genetics	Idiopathic Renal Failure on Young (5015)	171	WB: 3mL EDTA (lavender) tube	No	60 d	No	Yes	Inst, Self-Pay, Ins	P: 973-623-1264 E: info@cgcgenetics.com W: https://www.cgcgenetics.com
GeneDx	Nephrotic Syndrome/FSGS (TG99)	55	WB: 2-5 mL EDTA (lavender) tube (preferred); Buccal swab	Blood; Buccal	4 w	No	Yes	Inst, Self-Pay, Ins	P: 301-519-2100 E: zebras@genedx.com W: https://www.genedx.com
Invitae	Progressive Renal Disease (75000)	195	WB: 3 mL EDTA (lavender) tube (preferred); Saliva;	Blood; Saliva; Buccal	10-21 d	Yes	Yes	Inst, Self-Pay, Ins	P:800-436-3037 E: clinconsult@invitae.com W: https://www.invitae.com
Iowa Institute of Human Genetics	KidneySeq Comprehensive Panel	330	WB: 6mL EDTA (lavender) tube	No	30 d	No	No	Inst	P: 319-335-3688 E: clinicaldivision@healthcare.uiowa.edu W: https://medicine.uiowa.edu/humangenetics
	KidneySeq Glomerulopathies Panel	68							
Johns Hopkins DNA Diagnostic Laboratory	RenalZoom Glomerular Diseases and Complement Testing	118	WB: 3-6 mL EDTA (lavender) tube; Saliva	No	6-8 w	No	No	Inst, Self-Pay, Ins	P: 410-955-0483 E: ddl@jhmi.edu W: https://www.hopkinsmedicine.org/dnadiagnostic
Natera	Renasight	385	WB: 6 mL EDTA (lavender) tube; Buccal swab	Blood; Buccal	3 w	Yes	Yes	Inst, Self-Pay, Ins	P: 415-619-5054 W: https://www.natera.com
Prevention Genetics	Comprehensive Inherited Kidney Diseases (13990)	326	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube; DBS: 5 spots; Saliva	Blood, Saliva	18 d	No	No	Inst, Self-Pay, Ins	P: 715-387-0484 E: support@preventiongenetics.com W: https://www.preventiongenetics.com

Avg TAT = average turnaround time; d = days; DBS = dried blood spot; FSGS = focal segmental glomerular sclerosis; ins = insurance; inst = institution; WB = whole blood; w = weeks

1. Zhou Y, (2020) Chronic Kidney Disease. Springer. https://doi.org/10.1007/978-981-32-9131-7_1; 2. Knoers N, Nephrol Dial Transplant 2022;37:239-254; 3. Cocchi E, Clin J Am Soc Nephrol 2020;15:1497-1510; 4. de Haan A, Front Genet. 2019;10:1264; 5. Ortiz A, et al. Mol Genet Metab 2018;123:416–427; 6. Laney DA, J Genet Couns 2008;17:79–83; 7. Schiffmann R, Nephrol Dial Transplant 2009;24:2102–2111; 8. Smid BE, J Med Genet 2015;52:262-8; 9. Najafian B, Kidney Int 2011;79:663–670

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