# GENETIC TESTING: KIDNEY DISORDERS

## OVERVIEW

Inherited kidney disorders and inherited disorders that indirectly affect the kidneys can be more common, such as autosomal dominant polycystic kidney disease, or more rare, such as Lowe syndrome and Fabry disease. Identifying the genetic cause of an inherited kidney disorder can help direct treatment, inform family members, and contribute to the overall understanding of the genetic etiology of chronic kidney disease. More advanced next-generation sequencing, such as exome sequencing and comprehensive genetic testing panels are emerging as a first-line diagnostic method for patients with chronic kidney disease.

## POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

| Coverage Criteria Sections | Example Tests (Labs) | Common CPT Codes | Common ICD Codes | Ref |
|---|---|---|---|---|
| **Polycystic Kidney Disease** | | | | |
| Targeted Variant Analysis | PKD1 Targeted Mutation Analysis<br>PKD2 Targeted Mutation Analysis<br>PKHD1 Targeted Mutation Analysis | 81403 | Q61, N18 | 1, 2, 20, 21 |
| Single-gene or Multigene Panel Analysis | PKD1 Sequencing Analysis<br>PKD2 Sequencing Analysis<br>PKHD1 Sequencing Analysis | 81406, 81407, 81479 | | |
| | Autosomal Dominant and Recessive Polycystic Kidney Disease (ADPKD and ARPKD) Panel (PreventionGenetics) | 81404, 81405, 81406, 81407, 81408, 81479 | | |

| | | | | |
|---|---|---|---|---|
| | Expanded Polycystic Kidney Disease NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) | | | |
| **Comprehensive Kidney Disease Panels** | | | | |
| Comprehensive Kidney Disease Panels | RenaSight (Natera) | 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479 | N00-N08, N10-N16, N17-N19, Q61, R31 | 3, 4, 5, 6, 7, 13, 14, 15, 16 |
| | KidneySeq Version 4 Comprehensive Testing (Iowa Institute of Human Genetics) | | | |
| | Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) Panel (PreventionGenetics) | | | |
| | RenalZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital) | | | |
| **Donor-Derived Cell Free DNA for Kidney Transplant Rejection** | | | | |
| Donor-Derived Cell Free DNA for Kidney Transplant Rejection | Allosure Kidney (CareDx, Inc.) | 81479 | T86.11, T86.12, Z94.0 | 9, 10, 11, 12 |
| | Prospera (Natera) | | | |
| | Viracor TRAC dd-cfDNA (Viracor Eurofins) | 0118U | | |
| **Other Covered Kidney Disorders** | | | | |
| Other Covered Kidney Disorders | See list below | 81400-81408 | | 17, 18, 19 |

# OTHER RELATED POLICIES

This policy document provides coverage criteria for hereditary kidney disorders. Please refer to:

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems

- ***Genetic Testing: Hereditary Cancer Susceptibility*** for coverage criteria related to von Hippel Lindau (VHL) syndrome and other hereditary cancer syndromes.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to genetic testing for kidney disease that is not specifically discussed in this or another non-general policy.

# COVERAGE CRITERIA

## POLYCYSTIC KIDNEY DISEASE

### Targeted Variant Analysis

I. *PKD1*, *PKD2*, *GANAB*, *DNAJB11* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, *DNAJB11, or PKHD1*.

II. *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease is considered **medically necessary** when:

   A. The member has a sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1*.

III. *PKD1*, *PKD2*, *GANAB*, *DNAJB11,* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease is considered **investigational** for all other indications.

### Single Gene or Multigene Panel Analysis

I. *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **medically necessary** when:

A. The member has any of the following clinical features of polycystic kidney disease:

1. Multiple bilateral renal cysts
2. Cysts in other organs (especially the liver, seminal vesicles, pancreas, and arachnoid membrane)
3. Hypertension in an individual younger than age 35
4. Intracranial aneurysm
5. Bilaterally enlarged and diffusely echogenic kidneys
6. Poor corticomedullary differentiation
7. Hepatobiliary abnormalities with progressive portal hypertension
8. Congenital hepatic fibrosis (CHF) with portal hypertension,

II. *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81409, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications.

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## COMPREHENSIVE KIDNEY DISEASE PANELS

I. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **medically necessary** when:

A. The member has chronic kidney disease with an undetermined cause after undergoing standard-of-care workup studies (e.g., history and physical examination, biochemical testing, renal imaging, or renal biopsy), **AND**

B. The member meets at least one of the following:

1. Onset of chronic kidney disease under 40 years of age, **OR**
2. One or more first- or second-degree relatives with chronic kidney disease, **OR**
3. Consanguineous family history, **AND**

C. The member is being considered for a kidney transplant.

II. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications.

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## DONOR-DERIVED CELL-FREE DNA FOR KIDNEY TRANSPLANT REJECTION

I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation(81479, 0118U) (e.g., Allosure Kidney, Viracor TRAC) is considered **investigational** for all indications, including but not limited to:

A. Detection of acute renal transplant rejection
B. Detection of renal transplant graft dysfunction

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## OTHER COVERED KIDNEY DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following genetic kidney disorders to guide management is considered **medically necessary** when the

member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

A. Alport Syndrome
B. C3 Glomerulopathy
C. Congenital nephrotic syndrome
D. Cystinosis
E. Cystinuria
F. Fabry Disease
G. Genetic (familial) atypical hemolytic-uremic syndrome (aHUS)
H. Primary Hyperoxaluria

II. Genetic testing to establish or confirm the diagnosis of all other kidney disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

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# NOTES AND DEFINITIONS

1. Close relatives include first, second, and third degree blood relatives on the same side of the family:

    a. **First-degree relatives** are parents, siblings, and children

    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

# BACKGROUND AND RATIONALE

**Donor-Derived Cell-Free DNA for Kidney Transplant Rejection**

Kidney Disease Improving Global Outcomes (KDIGO)

The Kidney Disease Improving Global Outcomes (2009) issued guidelines for the care of kidney transplant recipients. The guidelines included the following recommendations:

- "We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)"
- "We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)"
- "We suggest kidney allograft biopsy every 7-10 days during delayed function. (2C)"
- "We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation. (2D)"
- "We suggest kidney allograft biopsy when there is new onset of proteinuria. (2C)"
- "We suggest kidney allograft biopsy when there is unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours. (2C)"

Renal Association

The Renal Association (2017) published clinical practice guidelines for the care of patients from the period following kidney transplantation until the transplant is no longer working or the patient dies, which included the following:

- Guideline 4.1 – "We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient (1C)"
- Guideline 4.6 – "We suggest that a serum sample be sent at the time of renal biopsy (for graft dysfunction) to look for human leukocyte antigen (HLA)-specific antibodies (2C)"
- Guideline 5.1 – "We recommend that early identification of graft injury is desirable to maximise the potential for intervention. A proactive and systematic approach should employed to manage graft dysfunction (1C)"
- Guideline 5.2 – "We suggest that renal function should be monitored at each clinic visit by assessment of serum creatinine and qualitative evaluation of urine protein

excretion by dipstick, supplemented by spot protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) if positive (2C)"

- Guideline 5.3 – "We suggest that renal biopsy is the optimal investigation for parenchymal causes of graft dysfunction where the cause is uncertain (2C)"

**Single-gene or Multigene Panel Analysis**

*Gimpel et al (2019)*

"Both the American and the European Society of Human Genetics consider presymptomatic testing of minors for conditions with adult-onset acceptable if preventive actions can be initiated before adulthood. Cohort studies in children with ADPKD show an elevated incidence of hypertension, proteinuria and left ventricular hypertrophy, which affect prognosis and are amenable to treatment19. Although these data are from tertiary referral centre populations and thus may be biased towards more severe cases, they demonstrate that a subgroup of children exists in whom preventive treatment may be beneficial."

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*Dudley et al (2019)*

"Guideline 1 - We recommend that parents or carers of children at risk of developing ADPKD should be offered information on ADPKD inheritance and potential benefits and harms of testing for ADPKD, by health professionals with specialist knowledge in this area.

Guideline 2 - We recommend that children and young people aged 5years and above with, or at risk of developing ADPKD, should have an assessment of blood pressure (BP) at least once every 2years.

Guideline 3 - We recommend that the decision to test for ADPKD in asymptomatic children and young people (CYP) at risk of developing ADPKD, should be undertaken jointly between health professionals and parents or carers and, wherever possible, the young person.

Guideline 4 - If testing is decided on, we suggest that either kidney ultrasound or genetic testing may be offered to asymptomatic children and young people at risk

of ADPKD, where testing has been agreed by parents or carers (and, wherever possible, the young person) and health professionals.

Guideline 5 - We suggest that, if asymptomatic children at risk of ADPKD do not have cysts on ultrasound, further ultrasound testing should be deferred until adolescence (15–18years), or later if preferred by the young person.

Guideline 6 - We recommend that if genetic testing is planned in children and young people at risk of ADPKD, identification of the mutation in the affected adult family member (if not already known) should be undertaken prior to testing the child or young person."

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