

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 | Targeted Mutation Analysis | 81403 | Q61, N18 | 1, 2 |
| Single-gene or Multigene Panel Analysis | Autosomal Dominant Polycystic Kidney Disease via the PKD1 Gene (PreventionGenetics) | 81407, 81479 | | |
| | PKD2 Full Gene Sequencing and Deletion/Duplication (Invitae) | 81406, 81479 | | |
| | Autosomal Recessive Polycystic Kidney Disease (ARPKD) via the PKHD1 Gene (PreventionGenetics) | 81408, 81479 | | |

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|---|--|--|-------------------------------------|---------|
| | Autosomal Dominant Polycystic Kidney Disease (ADPKD) via the GANAB Gene (PreventionGenetics) | 81479 | | |
| | Autosomal Dominant Polycystic Kidney Disease (ADPKD) via the DNAJB11 Gene (PreventionGenetics) | | | |
| | Hereditary Cystic Kidney Diseases Panel (PreventionGenetics) | 81404, 81405, 81406, 81407, 81408, 81479 | | |
| | Polycystic Kidney Disease Panel (GeneDx) | 81406, 81407, 81408 | | |
| Comprehensive Kidney Disease Panels | | | | |
| Comprehensive Kidney Disease Panels | RenaSight (Natera) | 81407, 81363, 81406, 81479 | N00-N08, N10-N16, N17-N19, Q61, R31 | 3 |
| | KidneySeq Version 45 Comprehensive Testing (Iowa Institute of Human Genetics) | 81455 | | |
| | RenalZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital) | 81479 | | |
| 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 | 7 |
| | Prospera Kidney (Natera) | | | |
| | Viracor TRAC dd-cfDNA (Viracor Eurofins) | 0118U | | |
| Other Covered Kidney Disorders | | | | |
| Other Covered Kidney Disorders | See list below | 81400-81408 | | 4, 5, 6 |

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* (81408, 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* (81408, 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 (81407, 81455, 81363, 81406, 81479) is considered **medically necessary** when:

- A. The member has chronic kidney disease with an undetermined cause after undergoing standard-of-care workup studies (examples: 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 (81407, 81455, 81363, 81406, 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) 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

Polycystic Kidney Disease

GeneReviews: Polycystic Kidney Disease, Autosomal Dominant and Polycystic Kidney Disease, Autosomal Recessive

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended polycystic kidney disease testing for autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) is as follows:

“ADPKD should be suspected in individuals with the following:

- Multiple bilateral renal cysts and the absence of manifestations suggestive of a different renal cystic disease
- Cysts in other organs, especially the liver, but also seminal vesicles, pancreas, and arachnoid membrane...
- Hypertension in an individual younger than age 35 years
- An intracranial aneurysm...”

“Autosomal recessive polycystic kidney disease (ARPKD) should be suspected in individuals with bilaterally enlarged, diffusely echogenic kidneys...[and] one or more of the following:...Clinical/laboratory signs of congenital hepatic fibrosis (CHF) that leads to portal hypertension...”

“The renal diagnostic criteria for ARPKD detected by ultrasonography are:

- Increased renal size (in relation to normative size based on age and size of the affected individual);
- Increased echogenicity;
- Poor corticomedullary differentiation”

“[In] Childhood and young adulthood...The hepatobiliary abnormalities with progressive portal hypertension are often the prominent presenting features.”

Comprehensive Kidney Disease Panels

Hays et al (2020)

“We propose the following approach, based on a review of current literature and our practical experience... This approach assumes individuals have already undergone an initial nephrologic workup, including biochemical and serologic testing, imaging of the kidneys, and renal biopsy if indicated.

...[A]fter a negative or inconclusive initial workup, a patient is considered to have KDUE [kidney disease of unknown etiology] and may then be stratified according to the probability of a genetic disease. We consider higher probability patients as those with the following risk factors: early-onset disease (age <40 years), a positive family history of CKD [chronic kidney disease], consanguinity, extrarenal anomalies, cystic renal disease, or congenital nephropathy.”

Donor-Derived Cell-Free DNA for Kidney Transplant Rejection

Knight et al (2019)

A publication in the journal *Transplantation* entitled “Donor-specific Cell-free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review” stated the following:

In summary, donor-derived cfDNA shows promise as a biomarker for the detection of acute transplant graft injury. It has potential to reduce the need for protocol biopsy surveillance, allowing for a more targeted diagnostic approach. Detection of injury occurs before clinical manifestation, meaning that there is a window for earlier detection and treatment of AR [acute rejection] and other causes of graft injury with the potential to improve outcomes. It may also facilitate the detection of under-immunosuppression and find use as a tool for monitoring during immunosuppression minimization. Further studies

are required to validate the thresholds for further investigation and intervention, determine the optimum frequency for monitoring, and to identify whether prospective monitoring using dd-cfDNA can indeed improve transplant outcomes compared to current practice.

REFERENCES

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